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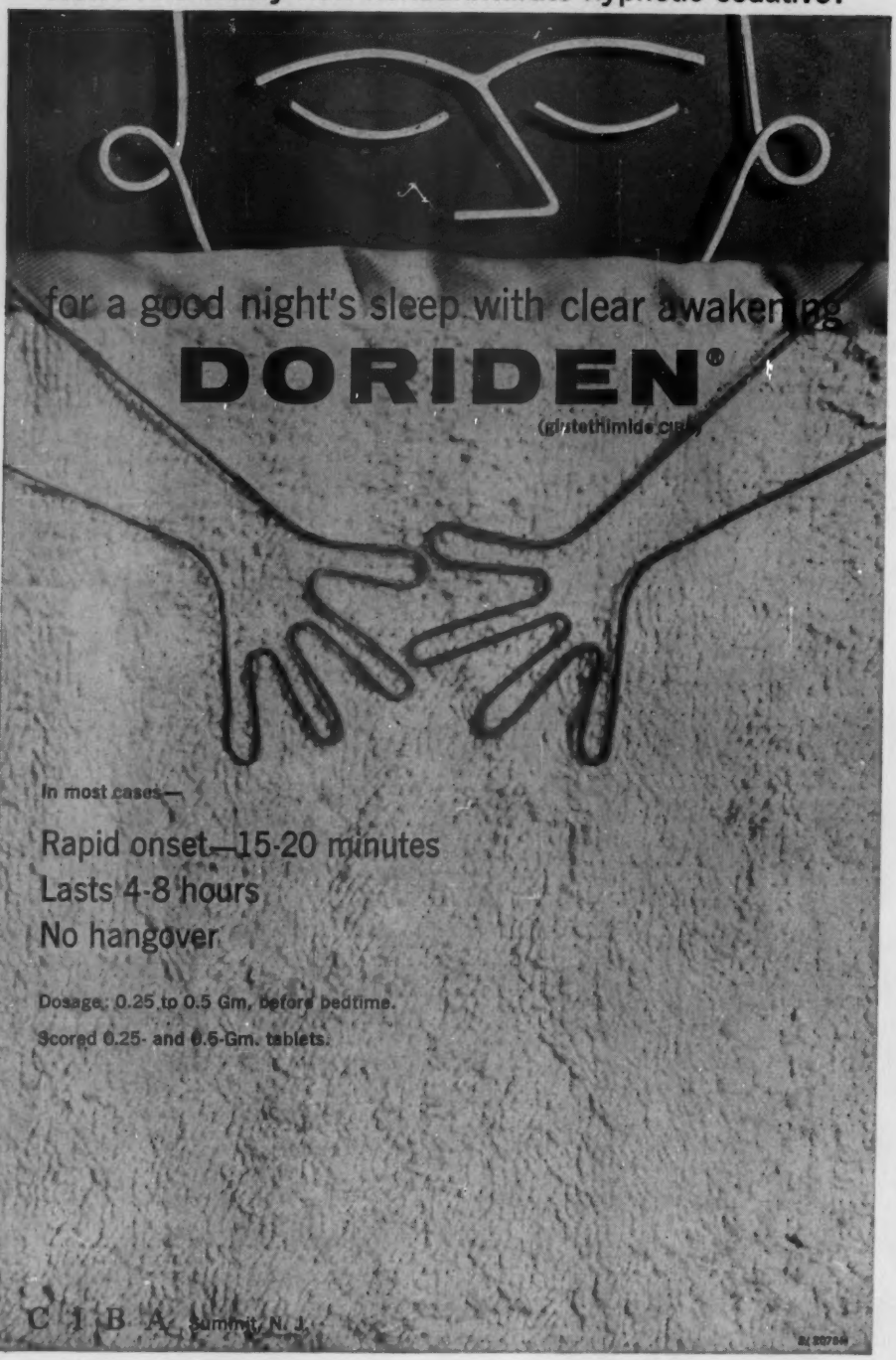
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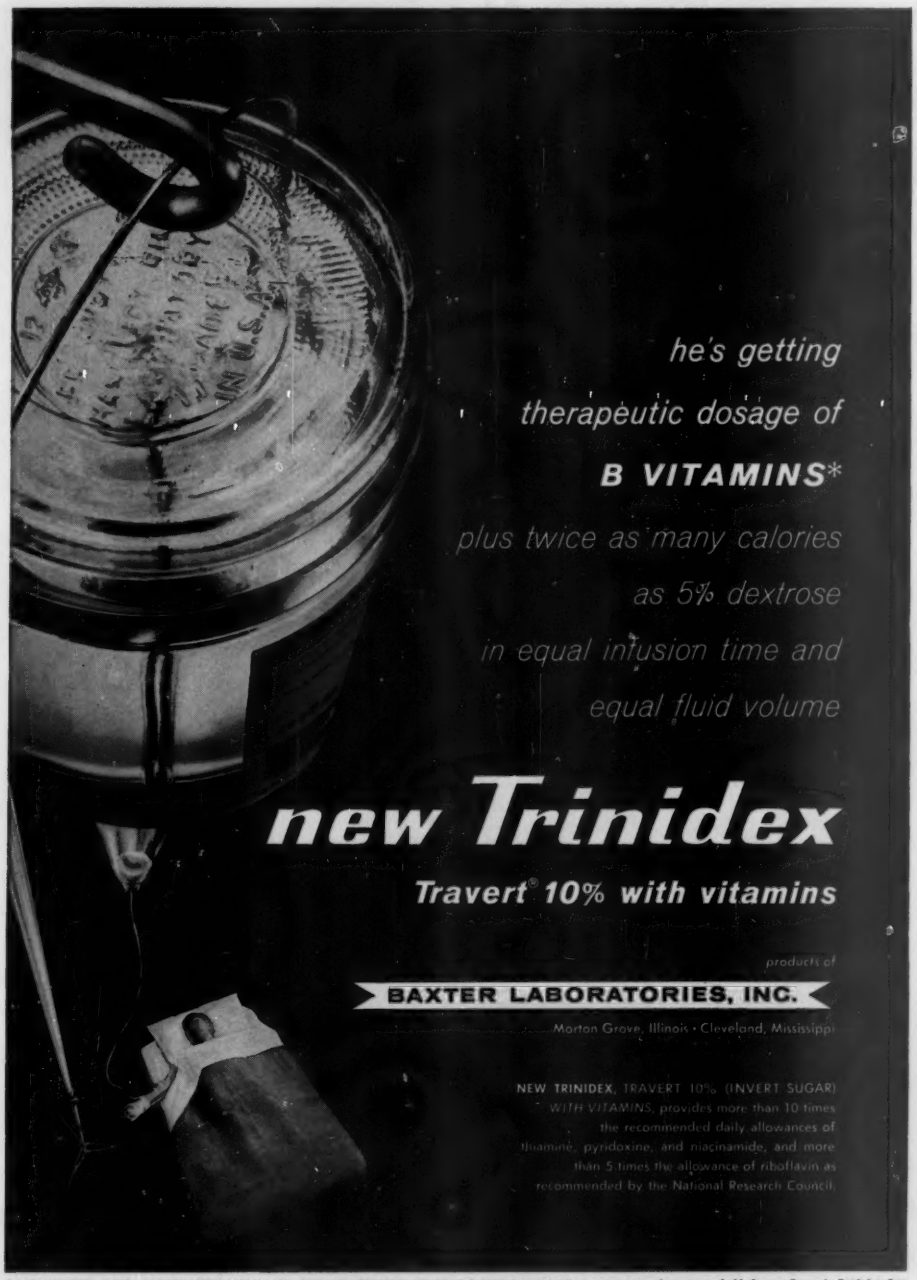
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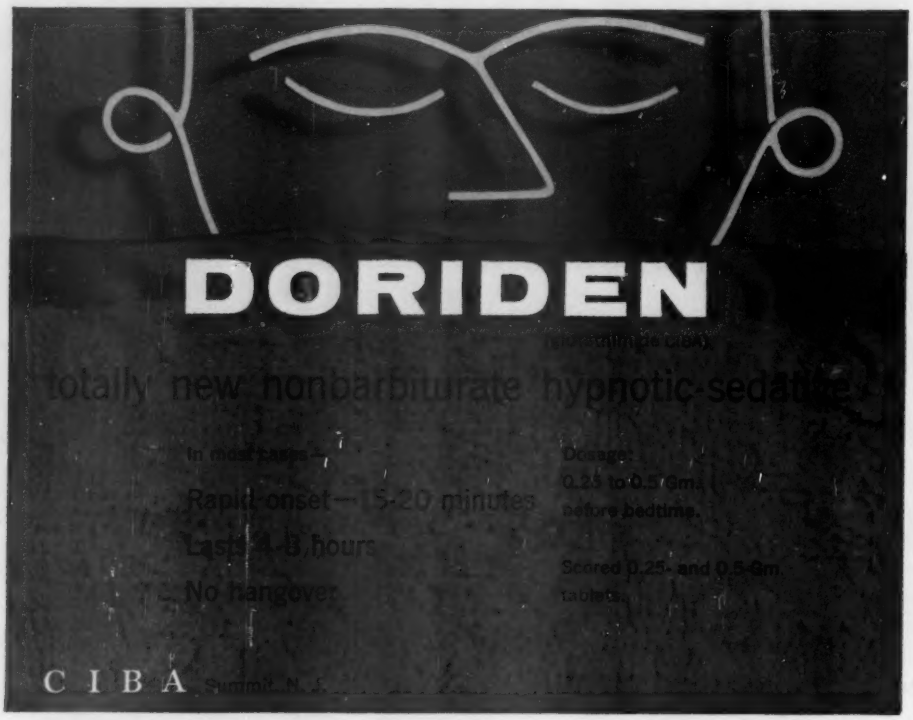

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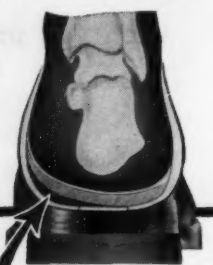

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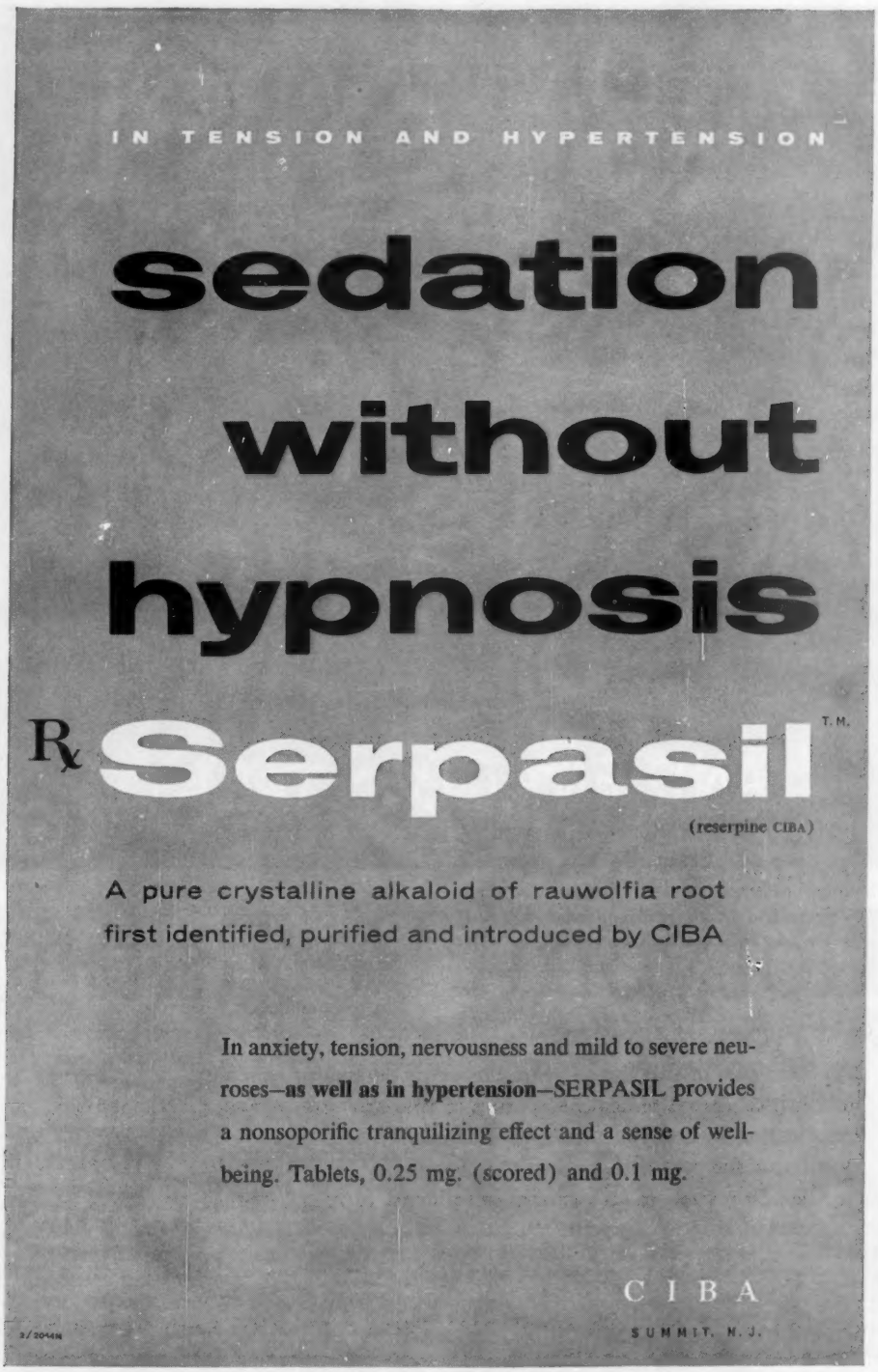
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Volume 252 JUNE 9, 1955 Number 23

POSTOPERATIVE MYOCARDIAL INFARCTION*

Report of Twenty-Five Cases

FRED WASSERMAN, M.D.,† SAMUEL BELLET, M.D.,‡ AND ROBERT P. SAICHEK, M.D.§

PHILADELPHIA

RECENT developments in anesthesia, wider use of antibiotics, improved postoperative care and the increasing percentage of older people in the general population[1-3] account for the performance of a wide range of operative procedures on older age groups, and on patients with known heart disease who are considered to be poor surgical risks. It is recognized that, in these groups particularly, cardiac complications before, during and after surgery present major hazards; of these, postoperative myocardial infarction is of considerable importance. In spite of the significance of this complication there have been relatively few detailed reports on this subject in recent years. The purpose of this paper is to emphasize the clinical manifestations, early recognition and treatment of postoperative myocardial infarction and to discuss certain facets concerning the precipitating causes and possible prophylaxis.

Space does not permit a complete review of the older literature; only the more significant and recent reports have been included for study. Postoperative coronary-artery occlusion has been reported by many authors.[4-10] That myocardial infarction may follow surgery on poor-risk patients is well known, and such cases have been described by various investigators.[7,11-14] The series of 35 cases reported in 1938 by Master and his co-workers[15] represents the largest group that we have been able to find. Recently, Davis et al.[4] observed 9 cases of postoperative coronary thrombosis, and in 1952 Wroblewski and LaDue[16] presented a detailed evaluation of 15 cases of postoperative myocardial infarction. We have collected a series of cases to review our experience in the present surgical, anesthetic and antibiotic era.

*From the Division of Cardiovascular Diseases, Graduate Hospital of the University of Pennsylvania.

This work was aided by a grant from the Foundation for Cardiovascular Research.

†Research fellow, Heart Association of Southeastern Pennsylvania.

‡Professor of clinical cardiology, Graduate School of Medicine, University of Pennsylvania; director, Division of Cardiovascular Diseases, Graduate Hospital, University of Pennsylvania.

§Resident in cardiology, Graduate Hospital, University of Pennsylvania.

METHOD OF STUDY

Twenty-five cases of postoperative myocardial infarction were collected at the Graduate Hospital between August 1, 1948, and August 1, 1954. Most of these cases were studied by one of us (S.B.) during the hospital course.

The data were analyzed for age, race and sex of the patient, preoperative status, anesthesia, type and duration of operation, blood pressure during and after surgery, postoperative course, clinical manifestations of the myocardial infarction, treatment and mortality. The electrocardiographic changes were carefully studied. The significant data are recorded in Tables 1 to 4.

The availability of preoperative and postoperative electrocardiograms for comparison helped make the diagnosis in 21 patients. Four patients had only postoperative tracings. These cases were included because the electrocardiograms showed changes compatible with acute myocardial infarction even though the clinical history provided no evidence of acute infarction during the preoperative period in the hospital. The return of these electrocardiograms to a normal or more normal configuration was regarded as evidence of healing of an acute process.

FINDINGS

Prevalence

During the interval between August, 1948, and August 1, 1954, approximately 37,000 major and minor operations were performed at the Graduate Hospital of the University of Pennsylvania. Of these, approximately 60 per cent were major, and the remaining 40 per cent were minor. The 25 cases of postoperative myocardial infarctions represent a combined rate of 0.07 per cent. It is noteworthy that 21 (0.1 per cent) of the 25 cases followed major and only 4 (0.03 per cent) minor operations. In spite of clinical manifestations suggestive of postoperative myocardial in-

farction a number of cases (10) could not be included in this series because the electrocardiographic changes

TABLE 1. *Types of Heart Disease Observed before Operation.*

TYPE	NO. OF CASES
Hypertensive cardiovascular disease	7
Arteriosclerotic cardiovascular disease	6
Hypertensive & arteriosclerotic heart disease	5
Rheumatic heart disease (mitral & aortic valves)	1
Total	19

were equivocal or because electrocardiographic or post-mortem verification was lacking.

Age and Sex

The average age of the 25 patients was sixty-four and six-tenths years, with a range of fifty to eighty years. There were 10 males and 15 females. Two of the males and 2 of the females were of the colored (3 Negro and 1 Chinese) race.

Preoperative Status

Of the 25 patients, 19 gave clinical evidence preoperatively of the various types of heart disease noted in Table 1. Eight of the 19 patients had evidence of the anginal syndrome, and 2 others gave electrocardiographic evidence of previous myocardial infarction. Of the 6 patients who presented no evidence of heart disease before surgery, 1 had mild diabetes mellitus, and 1 pulmonary fibrosis.

Only 10 patients were seen preoperatively by medical consultants; only 1 of these was considered a good risk, and 5 were considered fair, 1 poor to fair, and 3 poor risks.

TABLE 2. *Location of Operative Procedure.*

TYPE OF OPERATION	NO. OF CASES
Abdominal	17*
Pelvic	3
Thoracic	1*
Orthopedic	2
Other	3
Total	25

*In 1 case both chest & abdomen entered during operation.

Type of Operation and Anesthesia

Table 2 summarizes the data on the anatomic location of the operative procedure.

Twenty-one patients received general anesthesia; in 7 of these a muscle relaxant (such as curare) was used. Two patients received spinal anesthesia, and 2 were operated on under local anesthesia. The average duration of the operations was an hour and fifty minutes, with a range of thirty minutes to six hours.

Hypotension during Surgery

Twelve patients presented a decrease in blood pressure of 40 (or greater) systolic and 20 (or more) diastolic. The hypotension lasted five to thirty minutes, with an average duration of fourteen minutes. Six patients manifested slight blood-pressure depression that was not considered significant, and in 4 the level was sustained throughout the operation. No blood pressure was recorded during minor operative procedures on 3 patients.

Interval between Surgery and Infarction

In some cases, because of the obscuration of the clinical picture by analgesics and sedatives and the absence of electrocardiographic studies, it was difficult to determine exactly when the infarction had occurred. As far as we were able to determine, the diagnosis was established on the day of the surgery in 7 cases, on both the first and the second postoperative day in 3, on the third day in 1, on the fourth day in 2, on the fifth day in 1 and on the seventh day in 2. In 1 patient each the myocardial infarction occurred sometime between the day of surgery and the first postoperative day, the operative day and the second postoperative day, the operative day and the third postoperative day and the operative day and the fifth postoperative day. The infarction occurred on the thirteenth day in 1 patient and on the fourteenth in another. In summary this complication took place in 23 patients (92 per cent) on the day of or within the first seven days of surgery and occurred during the second postoperative week in the remainder. Myocardial infarction after the second postoperative week was considered unrelated to the surgery, and such cases were not included in this study.

TABLE 3. *Manifestations of Myocardial Infarction.*

SIGN OR SYMPTOM	NO. OF CASES
Pain:	
Typical	8
Atypical	4
Persistent hypotension	16
Dyspnea	6
Cyanosis	7
Diaphoresis	6
Congestive heart failure	5
Arrhythmia	5
Other:	
Weakness	2
Ashen pallor	1

Clinical Picture

Only 8 of the 25 patients presented the typical, severe precordial or substernal pain accompanied by a sensation of substernal oppression or constriction. Four of this group manifested a persistent hypoten-

sive state consisting of a drop of systolic blood pressure below 90. In 4 other patients the pain was atypical in that it was located in the left shoulder, right side of the chest or high in the midepigastrium; 2 of this group had hypotension. In the remaining 13 patients the characteristic clinical picture of myocardial infarction (unrelated to surgery) was not present.[15,17-21] Pain was absent in 10 of this group, but a significant hypotension was nevertheless present. In the remaining 3 there was neither pain nor hypotension. These data suggest that the usual clinical manifestations of infarction are observed in only about 50 per cent of the cases in the postoperative period. The typical pain was present in about 33 per cent. Hypotension was apparently a more important manifestation than the pain, having been observed in 16 (64 per cent) patients. Other manifestations, such as dyspnea, cyanosis and congestive heart failure (Table 3), point to the possibility of cardiac involvement but by themselves are not characteristic of infarction.

Three of the patients in whom arrhythmias developed showed frequent premature atrial contractions; 1 had a nodal rhythm, and 1 atrial fibrillation. None of these 5 patients had rapid ectopic rhythms.

Mortality

Five of the 25 patients (20 per cent) died during the period of observation. Three of the 5 deaths were the direct result of the myocardial infarction; in 2 the presence of other serious diseases (uremia in 1 and septicemia with severe electrolyte imbalance in the other) contributed to the death. In a patient who died thirty minutes after operation, the diagnosis was confirmed by post-mortem examination. Of the remaining 4, death occurred on the fifth day (fourth day after infarction) in 1, on the tenth day (day of infarction) in 1, on the eleventh day (eleventh day after infarction) in 1 and on the eighteenth day (fifth day after infarction) in 1.

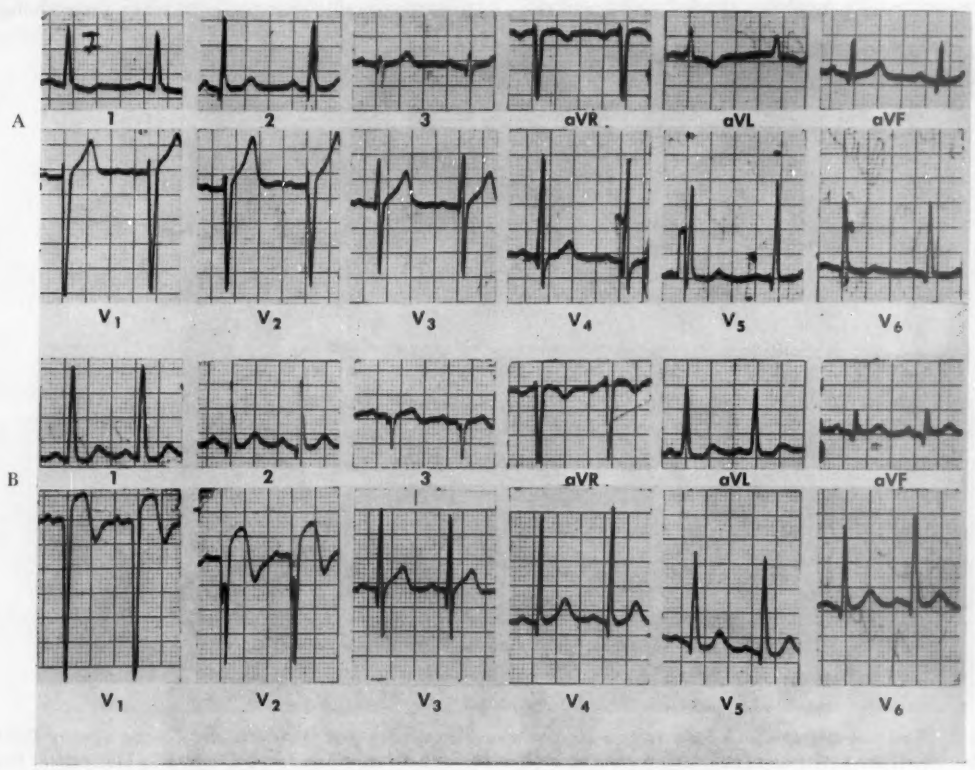

FIGURE 1. *Electrocardiograms in R.F., a Sixty-Seven-Year-Old Woman with Aortic Stenosis (Rheumatic?). Preoperative electrocardiogram* (A) *shows the changes in the QRS complex, ST segment and T waves suggestive of hypertrophy of the left ventricle and myocardial damage. Tracing* (B) *taken on the day after surgery (left-sided hemicolectomy) shows the RST-segment elevation, terminal T-wave inversion and QS configuration in Leads V_1 and V_2, suggestive of acute anteroseptal infarction.*

DISCUSSION

Electrocardiogram

The electrocardiographic changes observed were considered characteristic or suggestive of myocardial

infarction.[22-27] The cases of this series were divided as follows: patients with transmural infarction involving the anterior, posterior or lateral (or all three) portions of the left ventricle (9 cases), who showed QS patterns accompanied by RS-T-segment deviation in the limb and precordial leads considered characteristic of the sites involved (Fig. 1); and those with electrocardiographic alterations consisting of RS-T-segment deviations and serial T-wave changes (15 cases) — 12 of these showed inverted T waves of the coved variety involving Leads 1 and 2 and the precordial leads, extending from V_1 or V_2 to V_6. The RS-T segments were occasionally elevated (3 cases) in several of the precordial leads (Fig. 2). Three other patients had the combination of RS-T-segment depression and T-wave inversion in the precordial leads (Fig. 3).

The group consisting of inverted T waves is probably best regarded as subendocardial infarction, although slight epicardial involvement cannot be ruled out. These abnormalities were considered to be due to ischemic and anoxic changes (resulting from the hypotension) leading to the production of subendocardial necrosis (infarction), often without occlusion of a major coronary artery. Postoperative electrocardiograms on 3 of the patients who later died showed the changes characteristic of this group. All cases in the group were carefully reviewed to exclude so far as possible other conditions that could produce similar RS-T segment depression and T-wave inversion. The following conditions were considered in the differential diagnosis:

Pulmonary embolism was excluded by the absence of the characteristic changes in the QRS complexes and T waves in the limb and precordial leads,[13,28-33] the relatively long persistence of electrocardiographic changes, even when these changes followed a transient hypotension, and the absence of pulmonary signs. Occasionally, when accompanied by severe shock, pulmonary embolism may precipitate myocardial infarction.[19,34-36] This combination was observed in 1 of our cases. Secondly, electrolyte imbalance, particularly hypokalemia, can produce T-wave changes closely simulating those of myocardial infarction of the subendocardial type.[37] The similarity of the abnormal electrocardiographic tracings is probably due to myocardial changes that occur in the subendocardial zone of the myocardium. Hypokalemia was ruled out in these cases by the presence of normal serum potassium. Thirdly, the post-tachycardia syndrome can cause electrocardiographic abnormalities that are sometimes similar to those described above.

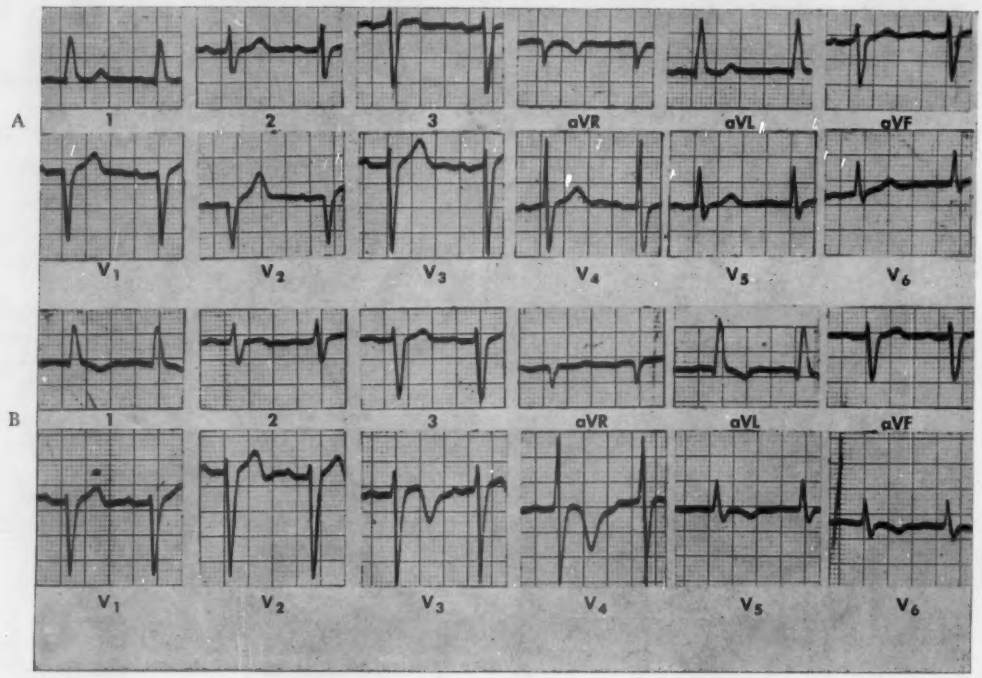

FIGURE 2. *Electrocardiograms in R.F., a Seventy-Six-Year-Old Woman with Arteriosclerotic and Coronary-Artery Disease. Preoperative electrocardiogram* (A) *shows intraventricular-conduction delay and myocardial damage. (This patient had a cholecystectomy and common-duct exploration.)*

Postoperative tracing (three days after surgery) shows slight ST-segment elevation in Leads V_1 to V_4 and T-wave inversions in Leads 1, aVL and V_3 to V_6.

However, none of the patients in this series manifested a rapid ectopic rhythm. Fourthly, after thoracic operations, particularly those in proximity to or entering the pericardium, an acute pericarditis may occur. The resultant RT-segment and T-wave changes may be mistaken for myocardial infarction. No such cases were included in this series.

Finally, certain drugs, especially digitalis, quinidine and vasopressor agents, may produce T-wave inversion. The cases were carefully reviewed, and the possible etiologic role of these drugs was excluded. When vasopressor substances were used the electrocardiogram was diagnostic before the agent was administered, or, if the electrocardiogram was not available before administration, the electrocardiographic changes persisted for weeks after the vasopressor drug was discontinued. In 2 cases in which both a vasopressor agent and digitalis were used, the presence of the characteristic QS configuration that had not been present in the preoperative electrocardiogram eliminated the drugs as causative agents.

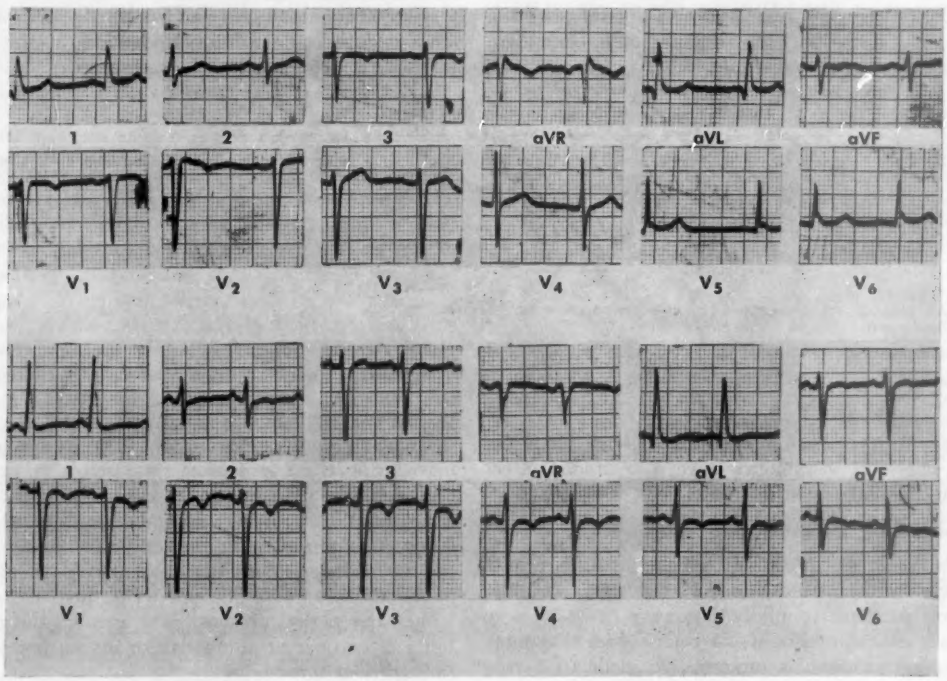

FIGURE 3. *Electrocardiograms in H.B., a Fifty-Two-Year-Old Woman with Hypertensive and Arteriosclerotic Heart Disease (Operation Consisted of Subtotal Gastrectomy and Cholecystectomy).*

Preoperative electrocardiogram (A) *suggests myocardial abnormality and hypertrophy of the left ventricle. In the tracing taken seven days after surgery* (B) *there is slight ST-segment depression in Leads V_2 to V_4 and symmetrical T-wave inversion in Leads V_2 to V_6.*

Predisposing Factors and Pathologic Physiology

It is generally accepted that no patient, regardless of age, should be denied urgent or emergency surgery. Even in such cases, however, it has been pointed out that a delay of several hours, if possible, to institute necessary intravenous therapy and check the function of the heart and of the urinary tract, might be life saving.[38] On the other hand, when elective surgery is planned for the patient over fifty, a detailed study is essential to uncover any factors that might increase the operative risk[39,40] It is beyond the scope of this paper to discuss all the factors that might influence either the surgeon or the anesthesiologist in accepting a patient for operation or in modifying a standard operative procedure; however, the cardiac, vascular and other diseases that appear to predispose to postoperative coronary-artery occlusion are worthy of discussion.

The presence of cardiac enlargement and hypertension,[11,15,16] a previous myocardial infarction, angina pectoris, conduction disturbances[5,7,9-12,14-16,41,42] and congestive heart failure[10,11,43] have been shown to increase the possibility that myocardial infarction will complicate surgery. Of the valvular diseases of the heart, aortic stenosis is most frequently associated with postoperative infarction, and the risk seems to be slightly increased in the patient with aortic insufficiency. Syphilitic heart disease,[5,10] by narrowing the coronary orifices, enhances the likelihood of postoperative infarction. Rapid ectopic rhythms shorten

diastole and produce a relative coronary insufficiency while simultaneously increasing the oxygen need of the myocardium.[15,16] The metabolic diseases frequently associated with coronary-artery disease are gout, xanthomatosis and diabetes mellitus. In summary it may be said that pre-existing heart disease present in 76 per cent of our patients probably predisposed to the development of myocardial infarction after surgery.

Other factors may be involved directly or indirectly. The patient should be investigated for anemia[44] and polycythemia.[45] To minimize postoperative complications the state of hydration and electrolytes,[38] the nutritional status and the presence of infection are important in the period before surgery. Anxiety, fear, anger and other emotions tend to increase blood coagulability.[46-49] Antibiotics have little if any effect on the coagulability of the blood.[50,51]

TABLE 4. *Comparable Findings in Postoperative Myocardial Infarction.*

Source of Data	Period of Study	No. of Cases	Mean Age	Rate of Pre-Existing Heart Disease	Symptoms			Frequency of Infarctions During 1st 3 Postoperative Days	Mortality
					Substernal Pain	Dyspnea	Congestive Failure		
			yr.	%	%	%	%		%
Graduate Hospital (present report)	1948-1954	25	64.6	76	33	25	21	48	20
Memorial Hospital	1948-1951	15	62.0	67	27	7	33	60	40
Mount Sinai Hospital	1931-1937	35	62.0	91	40	34	—	51	66

Factors during Operation

Anesthesia. Preoperative medication allays apprehension and helps induction of anesthesia. In older patients particularly mildly depressive drugs seem to be most desirable since it has been shown that more potent agents used as preoperative medication may cause severe hypotension or respiratory difficulty, resulting in anoxia, and may be associated with anesthetic deaths without the usual distress signals. Various anesthetic agents, by their effect on the heart[9,53-55] and respiratory mechanism,[52,56-58] may cause anoxia, hypercapnia and hypotension, which predispose to myocardial infarction during or after surgery. The importance of continued oxygen inhalation during the postoperative period, or at least until the patient given general anesthesia reacts, has been emphasized.[57,59] Cases of postoperative myocardial infarction have been observed when spinal and local anesthetics were employed.[4,10-12,15,16,41] Hypotension is fairly common with spinal anesthesia, with which, as a rule, the sensorium is only slightly depressed so that several of the factors believed to be important before operation may again be involved (for example, anxiety and fear) in myocardial infarction. In our series myocardial infarction followed local anesthesia in 2 and spinal anesthesia in 2 patients.

The muscle-relaxant anesthetic agents are considered to be a factor in the marked increase in the anesthetic death rate independent of the physical condition of the patient.[1] Some of the untoward effects could be the result of the decreased venous return to the heart incident to the diminished excursions of the diaphragm, and the decrease in function of the abdominal and accessory muscles of respiration. As a consequence myocardial anoxia is more likely to occur. Deaths from these drugs have also been attributed to circulatory collapse.[1]

Hypotension. The most common causes of hypotension during surgery are hemorrhage, reflex effects of visceral manipulation and anesthesia. The hypotensive state leads to the production of thromboembolic phenomena in various portions of the body, particularly coronary occlusion. The following factors during the hypotensive state result in vascular occlusion: the reduction in the coronary blood flow[60]; the stasis and narrowing of blood vessels due to circulating epinephrine[61]; and, in addition to hemorrhage, the increased number of blood platelets[62] and reduced antithromboplastic activity of the plasma. The longer the period of shock, the greater the probability of coronary thrombosis[34] or myocardial infarction without thrombosis.

Factors after Operation

Tissue injury and subsequent absorption of breakdown products, increase in blood platelets and circulating fibrinogen play a part in postoperative thromboses.[43,45,62-65] Many of the factors operative before surgery are also important in the postoperative period. The necessity for frequent blood-pressure and pulse determinations during the hours immediately after surgery[66] cannot be overemphasized. Early recognition and treatment of the hypotensive state may prevent the myocardial infarction.

Comparison of the Data by Various Authors

Table 4 compares our findings with those observed at Mount Sinai Hospital[15] (1938) and Memorial Hospital[16] (1952), New York City.

For purposes of comparison only the 8 patients with typical substernal chest pain were included. If we included the 4 patients who manifested atypical pain the combined occurrence of pain and postopera-

tive myocardial infarction would be 48 per cent. In myocardial infarction unrelated to surgery the absence of pain is relatively unusual[21]; however, the fact that approximately 50 per cent of our patients experienced no pain appears to be similar to the findings observed in the other series.

The somewhat lower mortality (20 per cent) in our series compared with that reported from Memorial Hospital may reflect the fact that most of the patients (13 of 15) in the latter group had malignant neoplasms and surgery was considered mandatory. In the series from Mount Sinai Hospital 8 of the 23 deaths (34 per cent) were the direct result of the coronary occlusion. Peritonitis, pneumonia, sepsis and uremia accounted for the remaining 15 deaths in the preantibiotic era covered in that report.

Treatment

Regarding the prevention of myocardial infarction after operation, it is apparent that often little can be done by way of prophylaxis in many of these cases because of urgency of surgery and the high rate of pre-existing heart disease in the older age group of patients. Whenever time permits, however, a thorough cardiovascular survey should be made from the standpoint of the etiologic factors mentioned. This would assure as optimum a preoperative state as possible and alert the surgeon and the anesthetist to the possibility of a vascular complication. The early recognition and treatment of hypotension, arrhythmias and congestive heart failure is mandatory. In the presence of an increased cardiac risk only the planned operative procedure should be carried out. Fluid, blood and electrolyte balance after surgery should be carefully maintained.[67]

When a myocardial infarction has occurred the standard measures of therapy should be employed. Postoperative ambulation should usually be delayed for about two or three weeks after the infarction.

Summary

Although postoperative myocardial infarction is fairly common relatively few large series of cases on this subject have been reported in recent years. A series of 25 cases occurring after various types of surgical procedures is reported. The clinical picture, electrocardiographic criteria for diagnosis and differential diagnosis are discussed. A comparison is made with other series of myocardial infarction reported after surgery. Emphasis is placed, particularly, on pre-existing heart disease and hypotension during surgery and in the immediate postoperative period as factors predisposing to this postoperative complication. The early recognition and treatment of the hypotensive state is stressed as a prophylactic measure. Postoperative myocardial infarction is particularly important because of the increasingly large number of elderly and poor-risk patients now subjected to surgery.

We are indebted to Miss Joan Eichmann, who, under the direction of Miss Gertrude Hanauer, record librarian at the Graduate Hospital, rendered invaluable aid in the perusal of a large number of hospital records.

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SUCCESSFUL USE OF REGITINE (PHENTOLAMINE) IN THE DIAGNOSIS AND SURGICAL MANAGEMENT OF A CASE OF PHEOCHROMOCYTOMA*

An Appraisal of its Clinical Usefulness

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IT is estimated that 800 persons die yearly in the United States of complications of hypertension due to pheochromocytoma.[1,2] Smithwick and his associates[3] found 5 unsuspected cases of pheochromocytoma among a group of 1000 patients subjected to sympathectomy and adrenal exploration for hypertension. The increasing recognition that such a tumor may cause sustained as well as paroxysmal hypertension has led to the continued search for a simple and safe diagnostic agent for screening hypertensive patients. The recent introduction of Regitine by Grimson[4] and others[5,6] has made available an agent that has shown no serious side reactions to date.[7] To this advantage for diagnostic uses may be added the absence of periods of epinephrine-fast hypotension after removal of the pheochromocytoma, when Regitine has been used for blood-pressure stabilization before and during the removal of the tumor, in contrast to the adverse effects of benzodioxane in this situation.[8] An illustrative case study is presented.

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CASE REPORT

R.M. (U.C.H. 199818), a 30-year-old housewife, was first seen at the University of California Out-patient Department in March, 1952, complaining of profuse perspiration, which had begun during her 1st pregnancy 3½ years previously. Hypertension was noted at that time, as well as a genitourinary-tract infection that was treated with sulfonamides. After delivery the hypertension was said to have decreased; the sweating, however, had persisted and became more profuse after a 2d pregnancy in 1951, when she began to complain of episodic suboccipital headaches, choking sensations, heat intolerance, palpitation, irritability and insomnia. Thyrotoxicosis was apparently suspected in 1951, when a basal metabolic rate of + 72 per cent was reported. Treatment with propylthiouracil in doses of 200 mg. daily failed to lower the metabolic rate, which was still elevated (+ 62 per cent) in January, 1952, but the level of protein-bound iodine was normal. The patient was admitted to the University of California Hospital in May, 1952, with a presumptive diagnosis of pheochromocytoma.

Physical examination revealed a husky, healthy-appearing woman with a deep voice, who was perspiring heavily. The eyebrows were sparse; otherwise the hair distribution was normal. The ocular fundi gave no evidence of vascular abnormality. The thyroid gland was palpable, but not enlarged. There was slight cardiac enlargement on percussion, with a loud aortic 2d sound. Palpation showed no abnormal masses in the abdomen.

The temperature was 98.4°F., the pulse 78, and the respirations 20. The blood pressure was 190/120.

An x-ray film of the chest was regarded as normal; an electrocardiogram indicated hypertrophy of the left ventricle. The basal metabolic rate on three occasions varied between +45 and +75 per cent; the protein-bound iodine measured 4.6 microgm. per 100 cc. A 5-hour glucose tol-

erance test was within normal limits. In an attempt to establish a diagnosis of pheochromocytoma special studies (Fig. 1) were carried out. A sedation test with Amytal Sodium (0.2 gm. every hour for 3 doses) showed a fall of blood pressure to normal. A cold-pressor test produced a positive response; the blood pressure rose from a baseline of 170/100 to 220/140. The benzodioxane test (18.5 mg. given intravenously) caused no significant change in blood pressure; however, the baseline pressure was not markedly elevated. A Mecholyl test (10 mg. given subcutaneously) produced no response until approximately 6 minutes after administration of the drug, when the blood pressure had dropped from a baseline of 160/90 to 95/40, and the patient began to complain of severe, crushing substernal pain. She was therefore given atropine, 0.4 mg. subcutaneously. A subsequent electrocardiogram indicated T-wave inversion over Leads V_4 through V_6. Intravenous pyelograms showed normal kidney shadows, with no evidence of adrenal enlargement. Retroperitoneal oxygen studies were interpreted as showing no abnormalities in the adrenal areas, although the left side was poorly outlined.

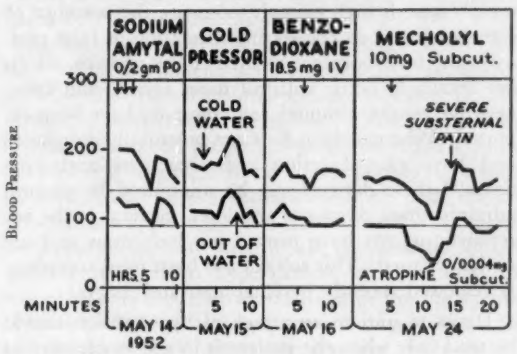

FIGURE 1. *Results of Various Tests for Pheochromocytoma, May 14 to 24, 1952.*

In view of the negative results of these studies a definite diagnosis of pheochromocytoma could not be made, and the patient was discharged on May 24. She was given a mild sedative and also Banthine in an attempt to control the excessive diaphoresis. She was then followed in the Hypertension Clinic,* continuing to complain of episodes of generalized headache, often associated with profuse perspiration, heat intolerance and palpitation.

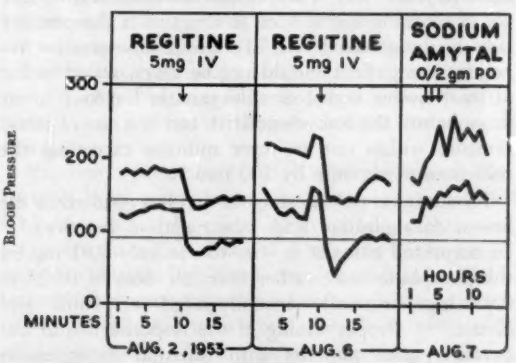

FIGURE 2. *Results of Various Tests for Pheochromocytoma, August 2 to 7, 1953.*

She was rehospitalized in July, 1953, because of sudden blurring of vision of the right eye. At that time the blood pressure had risen to 215/125 in both arms and 280/160 in the right leg; the pulse was 112. Funduscopic examination now revealed numerous flame-shaped hemorrhages bilaterally, hard exudates and moderate arteriolar spasm and arteriovenous nicking. The disks were flat but had indistinct margins. Renal studies showed a corrected creatinine clearance of 78.6 cc. per minute, a blood nonprotein nitrogen of 37 mg. per 100 cc. and a + test for albumin in the urine. The basal metabolic rate was + 56 per cent. An electrocardiogram showed hypertrophy of the left ventricle. Two Regitine tests (5 mg. administered intravenously) resulted in a drop in blood pressure from a baseline level of 195/130 and 230/150 to 130/80 and 140/70 respectively within 1 minute lasting over 10 minutes. There was a rise of blood pressure after a test with Amytal Sodium (Fig. 2), a finding completely different from that during the previous entry. Intravenous pyelograms now showed downward and outward displacement of the left kidney by a large oval mass. This was confirmed by a retroperitoneal oxygen study with tomograms (Fig. 3).

FIGURE 3. *Tomogram, Showing Displacement of the Left Kidney by Tumor (Retroperitoneal Oxygen Study).*

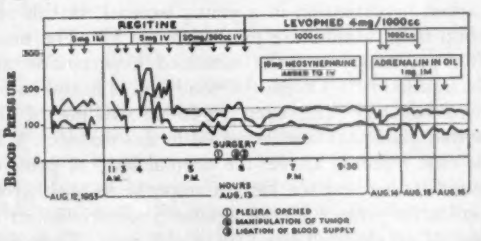

FIGURE 4. *Blood Pressure before, during and after Operation.*

Four days before operation the patient noted impairment of vision in the left eye. For this reason she was given 5 mg. of Regitine intramuscularly every 6 hours, with subsequent lowering of blood pressure. On the day of operation only 2 intramuscular injections were given; thereafter, the blood pressure was controlled with intravenous injections of Regitine (5 mg.) as needed. After premedication with 10 mg. of morphine and 0.4 mg. of atropine sulfate, anesthesia was induced with Pentothal Sodium and ether. An intravenous infusion of Regitine (20 mg. per 500 cc.) was continued during the operative procedure to prevent any paroxysmal rise in blood pressure (Fig. 4).

*We are indebted to the members of the Hypertension Clinic for making this patient available for clinical studies.

When the left suprarenal area was exposed through the usual flank approach a well encapsulated tumor was found anterior and medial to the upper pole of the left kidney. The mass was yellow, with several dilated veins on its surface. Further dissection revealed that it lay anterior to and separate from the left adrenal gland but was attached to it by a tongue of cortical tissue. The tumor was readily removed with complete hemostasis. Palpation of local and intraperitoneal structures (without opening of the peritoneum) revealed no other masses. Gross and microscopical examination showed the tumor to be a benign pheochromocytoma weighing 66.9 gm.

During the operation the blood pressure remained fairly stable at approximately 130/90. The continuous intravenous infusion of Regitine was maintained until the blood supply to the tumor was clamped. At that time the pressure dropped slightly; the Regitine infusion was immediately stopped, and an infusion of 4 mg. of Levophed (nor-epinephrine) per 1000 cc. of 5 per cent glucose in water was started. Later 10 mg. of Neo-Synephrine was added to this solution, which was continued until the 2d postoperative day. A total of 10 mg. of Neo-Synephrine and 8 mg. of Levophed were used. Epinephrine in oil (1 mg. intramuscularly) was then substituted and given for an additional 2 days (Fig. 4).

After the operation most of the symptoms disappeared, although the patient complained of generalized weakness for several weeks after removal of the tumor. There was subjective improvement in vision. She was discharged on the 9th postoperative day.

She has since been followed in the Medical Clinic for approximately a year, and is feeling well. The intense headaches and profuse perspiration have disappeared completely. The blood pressure has stabilized at 120/75, and electrocardiograms have shown serial changes toward normal. It is of interest that special studies of adrenocortical function performed before the operation showed a very low level of urinary 17-ketosteroids (less than 1 mg. per 24 hours) and 17-hydroxycorticoids (4 mg. per 24 hours) and subnormal responses to ACTH stimulation. In contrast, adrenocortical function gradually returned to normal 3 months after removal of the medullary tumor (17-ketosteroids 7.7 mg. and 17-hydroxycorticoids 5.8 mg. per 24 hours).

Discussion

Clinical Features

This case manifested many of the classic features of pheochrome tumors. Outstanding were the definite attacks of headache, the excessive sweating and marked hypertension in a young woman; in this age group these tumors are most common.[9,10] The onset after pregnancy and the sustained hypertension are not unusual.[11-13] Often, the condition is mistaken for thyrotoxicosis,[14] and even transient swelling of the thyroid gland has been reported in this disorder.[15] In the case reported above, the normal level of protein-bound iodine and the lack of response to antithyroid medication were evidence against hyperthyroidism in spite of an elevated basal metabolic rate. There was no family history of hypertension[16] and no stigma of neuroectodermal dysplasia (Hippel–Lindaus or Recklinghausen's disease), which at times are associated with pheochromocytoma.[17] The responses to the cold-pressor test and Amytal Sodium sedation, which seemed of value in the differentiation of pheochromocytoma from essential hypertension in a large series of patients studied by Smithwick et al.,[3] were misleading in our patient. Nevertheless, the clinical picture was so convincing that it led to a re-evaluation of the case and eventual cure.

Diagnostic Procedures

Pharmacologic tests. The agents used in these tests fall into two groups: substances, such as histamine, Mecholyl and TEAC, designed to release pressor substances from the tumor and thus to produce a paroxysm of hypertension, and substances, such as Dibenamine, benzodioxane and Regitine, designed to block these catechols, once released, and thus to produce a fall of pressure. The effectiveness of these compounds depends in large measure on proper timing (that is, a blocking agent should be used when the pressure is high enough to ensure the presence of catechols) and on correct interpretation of false-positive and false-negative results. False-positive results are known to occur with all these agents, and false-negative results, although less common, have been reported. Whereas these tests are potentially dangerous and have caused serious side reactions and even death,[18] these dangers can be minimized by prompt administration of proper antidotes. Several of the adrenolytic agents have proved too hazardous and are no longer used. This subject has been most completely reviewed recently by Chapman and Singh.[7]

Drugs to initiate an attack of hypertension should be used only when the patient is in a normotensive or low hypertensive state. Although their exact mode of action is not known, their common property is vasodilatation. This may increase secretion of pressor substances by the tumor and precipitate a paroxysm of hypertension. On the other hand the hypertension may represent an exaggerated response to the initially produced momentary fall in blood pressure. These drugs are potentially dangerous and can precipitate cerebrovascular accidents or congestive heart failure, especially in elderly patients. These risks can be reduced somewhat by use of smaller doses and by free use of blocking agents such as Regitine if the pressure rises to dangerous levels. To avoid false-positive reactions the patient should not be given sedatives for at least twelve hours, or thiocyanates for four to six days, before the test. A positive test is a rise of blood pressure within one to three minutes exceeding the cold-pressor response by 100 mm.[19-21]

Histamine is the safest agent and has resulted in the fewest false-positive and false-negative reactions.[7,22] In suspected cases it is wise to use only 0.01 mg. of the phosphate base, rather than the dose of 0.025 to 0.05 mg. originally recommended by Roth and Kvale.[23,24] Proper timing of the response is also important, since patients with essential hypertension may show a rise in blood pressure four to ten minutes after injection of histamine.[22] Our patient was in a normotensive state on only one occasion, at which time, unfortunately, Mecholyl was used instead of histamine.

Mecholyl is probably not as reliable as histamine and is more dangerous; its action is slower and more prolonged.[25] Doses of 10 to 25 mg. subcutaneously have been recommended for initiating an attack. The

patient should be given 1 mg. of atropine sulfate before the injection; fatal reactions have occurred when this step was omitted.[11] Our patient showed a false-negative reaction, with a marked fall rather than the expected rise of blood pressure. Subsequently, there were subjective and electrocardiographic changes of myocardial ischemia, from which she later recovered.

TEAC (tetraethyl ammonium chloride)[25] is no longer used because of greater unreliability and side-reactions.

DMPP (1, 1-dimethyl-4-phenylpiperazinium iodide), a recently developed agent, has been advocated by Page and McCubbin.[26]

Agents that lower the blood pressure should be used when the patient is in a definitely hypertensive state — that is, with blood-pressure readings of 170 systolic, 110 diastolic, or higher.[21] Their action in lowering the blood pressure depends on either chemical blocking of ganglions or on the peripheral action of the released pressor substances, or on both. Since Dibenamine apparently does not reverse the action of nor-epinephrine and since it will decrease the blood pressure in essential hypertension, it is of doubtful value; thus, benzodioxane and Regitine are the agents of choice.[7,20] A fall in blood pressure of more than 35 systolic, 25 diastolic, or to normotensive levels within several minutes, represents a positive result.

Benzodioxane, which was initially introduced by Fourneau and Bovet[27] in 1933, has been used since 1947 as a diagnostic test agent in doses of 0.25 mg. per kilogram of body weight or 0.01 gm. per square meter of body surface given intravenously over a two-minute period.[28,29] It frequently causes unpleasant subjective symptoms, such as warmth, palpitation and apprehension, with flushing and sweating, and occasionally produces severe hypertensive crises in patients with essential hypertension.[18,30] Although the test is well standardized, false-positive reactions are not uncommon, especially if the patient is uremic, and false-negative reactions, as in the case reported above, are not rare.[7,31] It should be noted, however, that the patient was only mildly hypertensive at the time of this test.

Regitine (phentolamine)[4] blocks the pressor effects of both epinephrine and nor-epinephrine.[6,32,33] The drug should be given intravenously, rather than intramuscularly,[6] in doses of 5 mg. for adults and 1 mg. for children. Regitine is the safest of the available adrenolytic agents, is active when administered orally or parenterally and causes few side effects, other than mild tachycardia. In our patient the drug produced a typically positive reaction. Unlike benzodioxane it tends to depress the blood pressure slightly in essential hypertension. Only 1 false-negative response to the intravenous Regitine test has been described to date.[4,7] False-positive reactions, however, have been more common with Regitine than with benzodioxane, particularly in patients under sedation and those with uremia or with slightly elevated blood pressures, who become normotensive after administration of the drug. Positive tests should be carefully checked by other available methods to avoid unnecessary exploratory operations.

X-ray visualization. An occasional tumor can be detected on plain films through the presence of calcifications within the capsule. Of 11 proved cases of pheochromocytomas, only 1 was visualized by pyelography.[3] The fact that these tumors may occur in extra-adrenal locations makes this method even less reliable.[21,34] Although perirenal air insufflation has generally been abandoned because of its hazards, visualization by the presacral oxygen insufflation method of Rivas as modified by Steinbach et al.[35] has proved accurate in localizing both adrenal and extra-adrenal tumors. The extra-adrenal tumor in the case described above was well demonstrated by this technic (Fig. 3). If the area is not adequately visualized, tomograms will help detect a tumor. Unfortunately, not all tumors are visualized, and other round structures may be mistaken for pheochromocytoma, especially in a patient with a suggestive history and a positive screening test. This has led to unnecessary exploration of a patient with renal cyst[30] and another patient with an accessory lobe of the liver.[37]

Direct estimation. The direct estimation of catechols such as epinephrine and nor-epinephrine in blood and urine, as reported by Engel and von Euler,[38] von Euler[39] and Goldenberg et al.,[40] promises to be a most reliable test for pheochromocytoma. To date, most patients with pheochromocytoma have shown much higher levels of catechols than normal subjects.

Treatment

The complete surgical removal of a pheochromocytoma, the treatment of choice, has carried mortality rates ranging from 15 to 37 per cent in the past.[20,41,42] An excessive surgical risk exists at two stages of the procedure: before and just after removal of the tumor.

Period before removal of the tumor. The advent of safe and effective blocking agents such as Regitine has considerably decreased the surgical risk[43-46] by preventing paroxysms of hypertension. The dangers of precipitating paroxysms during induction of anesthesia can be minimized as well by effective blocking of the pressor agents. Cyclopropane and chloroform, which enhance the development of cardiac arrythmia in the presence of high blood levels of epinephrine, should not be used.[47,48] Adequate exposure, careful visualization and cutting of the venous drainage from the tumor before handling are imperative,[44] especially without the use of protective blocking agents. The occurrence of mild adrenocortical depression in the presence of a pheochromocytoma[19,49] or the occasional presence of a tumor in both adrenal glands[16] may call for the use of 100 to 200 mg. of cortisone acetate on the day before, the day of and one or two days after surgery, with gradual reduction thereafter. The patient described above with-

stood Pentothal Sodium and ether well, required no cortisone and showed no undue rise in blood pressure during the intravenous infusion of Regitine (20 mg. in 500 cc.).

Period after removal of the tumor. A state of severe hypotension and shock may immediately follow removal of the tumor owing to sudden deprivation of adrenergic pressor substances. One may minimize this hazard by preventing paroxysms during operation[45] and by not using Dibenamine and benzodioxane preoperatively. Hypotension may be reversed by infusions of nor-epinephrine or epinephrine, and Pitressin is now rarely necessary.[8,20] No marked hypotensive phase was encountered during the management of the case presented above. The absence of persistent hypotension after surgery actually raises the suspicion of the presence of another tumor, of functioning metastases or of secondary, irreversible hypertension due to nephrosclerosis. Constant infusions of nor-epinephrine and Neo-Synephrine are usually required for several days in decreasing quantity; epinephrine in oil may then be substituted as in this case (Fig. 4). A moderate lack of sensitivity to these pressor agents may occur temporarily in the postoperative state, and in some cases hypertonic glucose[19] and cortisone or hydrocortisone seem to potentiate the effectiveness of these agents.[50]

As in the case presented above, several patients with pheochromocytoma have been reported to show low levels of 17-ketosteroids in the urine.[19,49] About three months after removal of the medullary tumor this patient regained normal adrenocortical function. This phenomenon has no adequate explanation. "Exhaustion" due to continuous overstimulation of the adrenal cortex by epinephrine, as postulated by Shapiro et al.,[19] seems unlikely, particularly since Sandberg and his associates[50] have demonstrated that infusions of large amounts of epinephrine do not provoke release of adrenocortical hormone.

Summary

The use of Regitine in the diagnosis and operative management of a patient with the classic picture of pheochromocytoma is discussed. The diagnosis, though suspected on clinical grounds, could not be established before the use of Regitine owing to a succession of false-negative tests. After a positive Regitine test at a second admission the tumor was localized in its extra-adrenal position by the use of retroperitoneal oxygen studies combined with tomograms.

Successful removal of the tumor was carried out, with the use of Regitine before and during operation, and persistent epinephrine-fast hypotension and shock in the postoperative state were thus avoided.

The patient showed relative adrenocortical underactivity before operation, with return to normal function three months after removal of the medullary tumor.

The diagnostic and therapeutic steps are reviewed in the light of recent advances in this field.

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CORRELATION OF PULMONARY ARTERIOLAR RESISTANCE WITH PULMONARY VASCULAR CHANGES IN PATIENTS WITH MITRAL STENOSIS BEFORE AND AFTER VALVULOTOMY*

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IT has been suggested[1,2] that severe pulmonary changes, supposedly irreversible, in patients with mitral stenosis would preclude beneficial results from valvulotomy. Recent publications from this laboratory and elsewhere[3,4] indicate a more optimistic outlook. The present study is an attempt to throw light on this problem by comparing preoperative and postoperative cardiac-catheterization data with histologic changes in lung biopsies obtained at operation.

METHOD

Fifty patients with mitral stenosis (16 males and 34 females) are included in this study. All were incapacitated by dyspnea on slight exertion or were in jeopardy from bouts of pulmonary edema, hemoptyses or recurrent peripheral emboli. All but 4 were operated on by one of us (J.G.S.), and the remainder by Dr. Richard Warren, of the Veterans Administration. In each case a lung biopsy was taken from the anterior border of the left upper lobe. Cardiac-catheterization data were obtained on all patients before and on 16 five to twenty-eight months after operation. Heart catheterization was performed in the usual manner.[3] Pulmonary arteriolar resistance was calculated by the following formula:

$$\text{P.A.R.} = \frac{\text{P.A.P.} - \text{P.C.P.}}{\text{C.I.}}$$

where P.A.R. is the pulmonary arteriolar resistance, expressed in arbitrary units (normal is less than 5), P.A.P. is mean pulmonary-artery pressure in millimeters of mercury, P.C.P. is pulmonary "capillary" pressure in millimeters of mercury, and C.I. is cardiac index (that is, cardiac output expressed in liters per minute per square meter of body-surface area). The area of the mitral valve was estimated by the method of Gorlin and Gorlin.[5]

In addition to the routine hematoxylin and eosin stain, the lung biopsies were stained to demonstrate elastic tissue (Verhoeff) and alveolar basement membranes (periodic acid Schiff). Selected sections were also stained for connective tissue (Masson trichrome). The changes seen in the small pulmonary arteries less than 100 microns in diameter consisted exclusively of fibrous intimal thickening. These alterations (Fig. 1 and 2) were graded from 1 (normal) to 4 (severe) by one of us (F.G., Jr.) without previous knowledge of the other data.

RESULTS

Figure 3 compares the preoperative pulmonary arteriolar resistance with the degree of alveolar-wall fibrosis as seen in the lung biopsy in each of the 50 cases. Although there is no close correlation,** the 3

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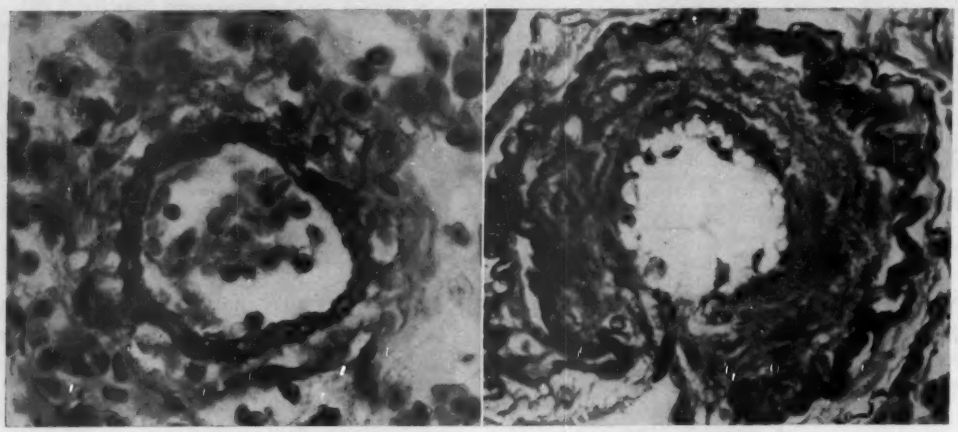
**By the Chi square test, if Chi square is greater than 3.84, the correlation is judged statistically significant. Correlation of pulmonary arteriolar resistance with alveolar walls was 3.45. Correlation of pulmonary arteriolar resistance with small vessels was 4.1.

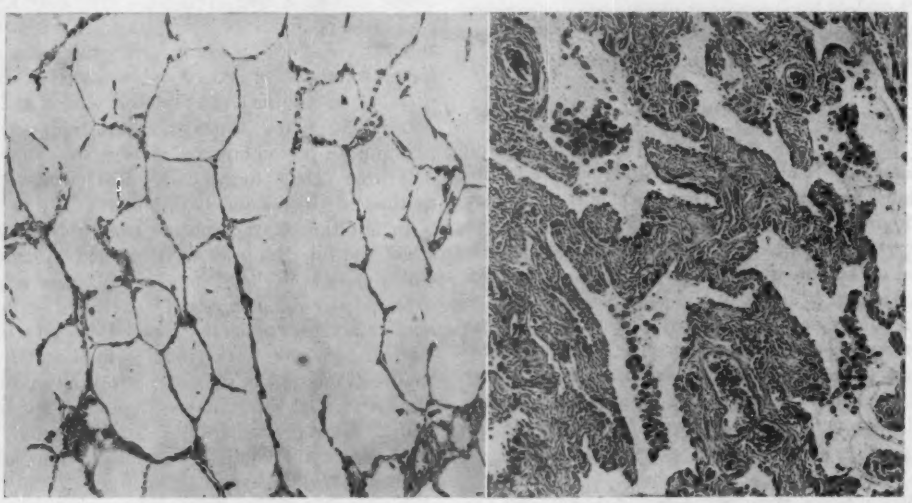
patients with the most marked alveolar-wall changes had the highest pulmonary arteriolar resistance. However, it is important to observe that among the patients with normal or only slightly involved alveolar walls, a considerable number showed a moderate or severe elevation of pulmonary arteriolar resistance.



A B

FIGURE 1. *Pulmonary Arteriole from a Normal Person* (A) *Compared with One from a Patient with Mitral Stenosis* (B), *Both Vessels Being Less than 100 Microns in Diameter (Verhoeff Elastic-Tissue Stain X 500). Note how marked fibrous intimal thickening partially occludes the lumen in B.*

Figure 4 compares the pulmonary arteriolar resistance with intimal thickening of the pulmonary vessels. Here, where one might have expected an excellent correlation, there was once again only rough agreement.* Although 3 of the 5 patients with the most severe vascular changes were in the group with the highest pulmonary arteriolar resistance, the lack of correlation was demonstrated by the fact that a considerable number of the patients with normal or only slightly involved small vessels were found to have significant elevations of pulmonary arteriolar resistance.



A B

FIGURE 2. *Section of the Lung from a Normal Person* (A) *Compared with That from a Patient with Mitral Stenosis* (B), *Showing Severe Fibrous Thickening of the Alveolar Walls (Hematoxylin and Eosin Stain X 125).*

*By the Chi square test, if Chi square is greater than 3.84, the correlation is judged statistically significant. Correlation of pulmonary arteriolar resistance with alveolar walls was 3.45. Correlation of pulmonary arteriolar resistance with small vessels was 4.1.

Sixteen patients were restudied by cardiac catheterization with an interval of at least five months after surgery. Initially, all the patients showed severe pulmonary hypertension.

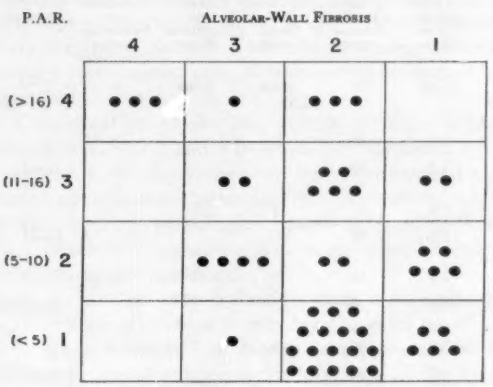


FIGURE 3. *Comparison of Pulmonary Arteriolar Resistance (P.A.R.) with Alveolar-Wall Fibrosis in 50 Patients with Mitral Stenosis.*
Each dot represents 1 patient.

Table 1 presents physiologic data before and after operation on the 4 patients with the greatest fall in pulmonary arteriolar resistance after valvulotomy. Three of these showed striking abnormalities of small vessels or alveolar walls or both. The results of the operation were excellent as judged both by objective criteria (significant rise in calculated mitral-valve area) and by gratifying clinical improvement.

abnormalities of the small vessels and alveolar walls. There was, however, a less satisfactory increase in

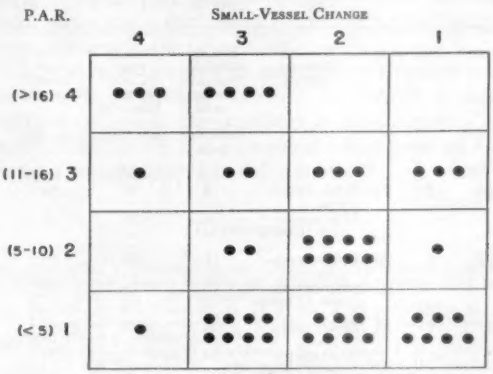


FIGURE 4. *Comparison of Pulmonary Arteriolar Resistance (P.A.R.) with Small-Vessel Changes in 50 Patients with Mitral Stenosis.*
Each dot represents 1 patient.

calculated mitral-valve area and a less impressive clinical response.

Table 3 gives the data for the 8 remaining patients, all of whom had normal or only slightly elevated pulmonary arteriolar resistance preoperatively.

Discussion

A few of the patients had normal small pulmonary vessels. The remainder showed varying degrees of fibrous intimal thickening. We are in complete agree-

TABLE 1. *Data before and after Valvulotomy in Cases with Greatest Fall in Pulmonary Arteriolar Resistance.*

Patient	Sex	Age	Time of Determination	Pulmonary Arteriolar Resistance	Pulmonary "Capillary" Pressure	Pulmonary-Artery Pressure	Cardiac Index	Estimated Mitral-Valve Area	Arterial Oxygen Saturation	Changes in Small Vessels	Changes in Alveolar Walls	Duration of Symptoms before Operation	Clinical Results
		yr.		*arbitrary units*	*mm./Hg.*	*mm./Hg.*	*liters/min./sq. meter*	*sq. cm.*	*%*	*grade*	*grade*	*yr.*	
D.H.	F	35	Before operation	20	34	75	2.0	0.4	96	4	4	7	
			After operation (10 mo.)	8	19	44	3.1	1.0	96				Excellent
J.L.	F	32	Before operation	13	25	50	1.9	0.5	93	1	1	2	
			After operation (8 mo.)	2	15	21	3.5	1.4	96				Excellent
P.F.	F	20	Before operation	8	29	50	2.7	0.9	97	4	2	3	
			After operation (9 mo.)	1	10	13	3.2	2.3	94				Excellent
E.R.	F	32	Before operation	9	26	50	2.8	0.6	95	2	3	7	
			After operation (26 mo.)	4	13	24	3.1	1.4	96				Excellent
Average			Before operation	13	29	56	2.3	0.6	95	2.8	2.5	4.8	
			After operation	4	14	26	3.2	1.5	96				

In Table 2 the data are given in 4 cases with less striking falls in pulmonary arteriolar resistance after operation. In common with the previous group these 4 cases showed marked pulmonary hypertension and

ment with Brenner[5] and with Parker and Weiss,[9] who did not find medial hypertrophy in the small pulmonary arteries, although this has been described by other authors.[2,4,6,7] When the the alveolar walls were

examined fibrosis was the only abnormality considered sufficiently reliable to compare with pulmonary arteriolar resistance. It would be of interest to correlate capillary engorgement, interstitial edema and emphysema with pulmonary arteriolar resistance, but not enough is known concerning artifacts introduced by the varying conditions under which the biopsies were taken. It is evident that there is no close agreement between the degree of elevation of resistance to blood flow through the lung and the magnitude of pathologic changes in the lung. This poor correlation suggests that vasoconstriction within the lung may be an important factor in producing pulmonary hypertension in mitral stenosis. The striking fall in pul-

TABLE 2. *Data in Cases with Less Striking Fall in Pulmonary Arteriolar Resistance.*

PATIENT	SEX	AGE	TIME OF DETERMINATION	PULMONARY ARTERIOLAR RESISTANCE	PULMONARY "CAPILLARY" PRESSURE	PULMONARY-ARTERY PRESSURE	CARDIAC INDEX	ESTIMATED MITRAL-VALVE AREA	ARTERIAL OXYGEN SATURATION	CHANGES IN SMALL VESSELS	CHANGES IN ALVEOLAR WALLS	DURATION OF SYMPTOMS BEFORE OPERATION	CLINICAL RESULTS
		yr.		*arbitrary units*	*mm./Hg.*	*mm./Hg.*	*liters/min./sq. meter*	*sq. cm.*	*%*	*grade*	*grade*	*yr.*	
L.B.	F	23	Before operation	6	34	54	3.7	0.9	89	2	1	6	
			After operation (6 mo.)	2	24	29	3.8	1.3	99				Good
E.P.	F	29	Before operation	11	28	60	2.8	0.9	92	2	3	3	
			After operation (5 mo.)	7	25	45	2.9	0.8	96				Good
M.V.	F	33	Before operation	18	33	56	1.3	0.2	90	3	3	10	
			After operation (9 mo.)	14	13	34	1.5	0.6	95				Excellent
J.B.	M	50	Before operation	19	24	60	1.9	0.5	90	3	2	6	
			After operation (9 mo.)	16	21	50	1.8	0.6	86				Poor
Average			Before operation	14	30	57	2.4	0.6	90	2.5	2.3	6.3	
			After operation	10	21	40	2.5	0.8	94				

TABLE 3. *Data in Cases with Normal or Slightly Elevated Pulmonary Arteriolar Resistance before Valvulotomy.*

PATIENT	SEX	AGE	TIME OF DETERMINATION	PULMONARY ARTERIOLAR RESISTANCE	PULMONARY "CAPILLARY" PRESSURE	PULMONARY-ARTERY PRESSURE	CARDIAC INDEX	ESTIMATED MITRAL-VALVE AREA	ARTERIAL OXYGEN SATURATION	CHANGES IN SMALL VESSELS	CHANGES IN ALVEOLAR WALLS	DURATION OF SYMPTOMS BEFORE OPERATION	CLINICAL RESULTS
		yr.		*arbitrary units*	*mm./Hg.*	*mm./Hg.*	*liters/min./sq. meter*	*sq. cm.*	*%*	*grade*	*grade*	*yr.*	
H.D.	F	36	Before operation	3	26	37	3.6	1.0	92	3	2	15	
			After operation (6 mo.)	1	14	16	3.5	1.5	97				Good
F.LaV.	F	32	Before operation	4	28	34	2.4	0.6	94	2	2	6	
			After operation (5 mo.)	2	14	18	2.5	1.1	97				Excellent
R.H.	M	41	Before operation	10	25	40	1.6	0.6	93	2	2	3	
			After operation (5 mo.)	8	19	35	2.1	0.8	96				Good
R.T.	F	42	Before operation	5	28	38	2.2	0.7	97	1	3	25	
			After operation (7 mo.)	4	9	20	2.8	1.9	96				Good
M.A.	F	45	Before operation	2	25	32	3.1	0.9	95	2	2	2	
			After operation (6 mo.)	1	11	15	3.4	1.9	94				Excellent
C.J.	F	37	Before operation	2	17	25	4.1	1.6	96	1	2	10	
			After operation (22 mo.)	2	30	41	4.6	1.3	96				Poor
R.S.	M	31	Before operation	1	29	35	4.2	1.1	95	2	2	3	
			After operation (6 mo.)	1	15	20	4.3	1.8	93				Excellent
M. A.	M	27	Before operation	6	24	38	2.3	0.6	95	2	1	5	
			After operation (28 mo.)	9	16	32	1.7	0.6	97				Poor

monary arteriolar resistance observed in some patients after operation is in keeping with this hypothesis. No correlation whatever was found between the pulmonary arteriolar resistance and large-vessel changes (over 100 microns), hemosiderosis, the presence or absence of atrial Aschoff bodies, pulmonary capillary pressure, mitral-valve area, arterial oxygen saturation, age of patient or duration of symptoms.

Consideration of the two groups of patients presented in Tables 2 and 3 in whom postoperative studies were made emphasizes the fact that marked elevation of pulmonary arteriolar resistance is reversible, despite striking pathologic changes in small pulmonary vessels or alveolar walls if an adequate valvulotomy can be accomplished.

When cardiac-catheterization data are compared with structural changes seen in lung biopsies the question arises whether the biopsy is representative of pathologic abnormalities in the lung as a whole. Four of the 50 patients in this series died after surgery. In these cases there was an excellent correlation of the biopsy with autopsy studies of the lung.

Summary and Conclusions

The pathologic changes in lung biopsies are correlated with cardiac-catheterization data in 50 patients operated on for mitral stenosis.

The lack of a close agreement between the degree of elevation of resistance to blood flow through the lungs and the magnitude of pathologic changes in the lungs suggests that vasoconstriction within the lungs may be an important factor in producing pulmonary hypertension in mitral stenosis.

Mitral-valve surgery in patients with severe pulmonary hypertension, whether or not they show marked structural abnormalities in the lung, may result in a striking fall in pulmonary blood pressure and a most satisfactory clinical result.

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TUBERCULIN HYPERSENSITIVITY IN TUBERCULOUS INFANTS TREATED WITH ISONIAZID*

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THE purpose of this paper is to record marked decrease of skin tuberculin hypersensitivity in 4 tuberculous infants during isoniazid therapy, and to discuss the possible implications of this phenomenon. Nine other cases are presented in which the hypersensitivity did not occur.

Observations

The group of cases in which tuberculin hypersensitivity was greatly diminished is described in Table 1. All 4 of these patients were under two years of age, were found to have positive skin reactions to old tuberculin (definitely positive Mantoux reactions to 1:1000 dilution) on contact examination and had normal roentgenograms of the chest. They were all treated with isoniazid alone in dosage of 8 mg. per kilogram of body weight per day. All patients became negative to old tuberculin in 1:100 dilution.

Table 1. *Reversion of Tuberculin Test from "Positive" to "Negative" in Patients on Isoniazid.**

Patient	Age at Beginning of Treatment	Period on Isoniazid before Conversion to Negative
	mo.	*mo.*
C.B.	7	6
D.L.L.†	10	7
J.Z.	8	6
E.A.	24	7

*All cases diagnosed on contact examination, without x-ray evidence of disease. Dosage of isoniazid, 8 mg. per kilogram of body weight per day.

†Streptomycin received along with isoniazid.

The second group, of 2 patients (Table 2), was similar clinically to the first, but these infants, at the

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end of five and six months of therapy, respectively, were still test sensitive to old tuberculin in 1:1000 dilution.

Finally, the third group, of 7 patients (Table 3), all with positive reactions to old tuberculin and with abnormal findings in roentgenograms of the chest, remained positive to a dilution of 1:1000 despite at least seven months of isoniazid at the same dosage level.

Testing was done with freshly prepared, standardized old tuberculin that had given satisfactorily positive reactions in other patients with tuberculosis. All 4 of the patients whose reactions changed from positive to negative were tested with 1:100 dilution of tuberculin prepared within a week of use. The material used was Lederle's concentrated old tuberculin diluted with a neutral phosphate buffer, a material that has been satisfactorily used at National Jewish Hospital for many years.

TABLE 2. *Patients without Reversion of Tuberculin Reaction on Isoniazid.**

PATIENT	AGE AT ONSET	PERIOD ON ISONIAZID AT LAST TUBERCULIN TEST
	mo.	mo.
B.N.	6	5
B.B.	27	6

*All cases diagnosed on contact examination, without x-ray evidence of disease. Dosage of isoniazid, 8 mg. per kilogram of body weight per day.

DISCUSSION

It has not previously been reported that tuberculous human beings treated with antimicrobial agents can become skin-test negative to 1 mg. of old tuberculin. In our experience[1] this occurred within less than eight months in 4 out of 6 infants who presented no roentgenographic evidence of disease in the chest at the time of initiation of therapy. Among 7 infants who had roentgenographic evidence of chest disease, no great loss of skin hypersensitivity to tuberculin was encountered during similar or longer periods of treatment.

Since the advent of the use of antituberculous drugs a decrease in the skin hypersensitivity to tuberculin has been noted in laboratory animals during or after treatment with either streptomycin or isoniazid.[2-4]

Conflicting reports have been published regarding the changing tuberculin test in human beings treated with streptomycin. Barnwell et al.[5] observed no change in the tuberculin sensitivity in 223 adult patients treated with streptomycin. Wetterwold[6] noted a diminution of the tuberculin reaction in 65.8 per cent of 79 tuberculous adult patients on streptomycin.

Varying reports have been presented regarding the changing skin hypersensitivity to tuberculin in tuberculous adult human beings with reinfection tuberculosis treated with isoniazid. Nobile and Biondi,[7] observing the tuberculin reactivity in 35 patients during isoniazid therapy, found an increase in sensitivity soon after initiation of treatment, followed by a decrease in sensitivity after five or six months in about two thirds of the patients showing clinical and roentgenographic improvement. Only a fourth of the patients who did not improve exhibited this change. Furthermore, only in a few cases did the decreased reactivity to tuberculin reach a point below that present before treatment. Hewell and Suyemoto[8] observed a significant trend toward decreased sensitivity to tuberculin (PPD-S) after one or two months of isoniazid treatment in 352 cases, followed by a later increase in sensitivity. Criep and Levine[9] found no change in the tuberculin reaction in a series of tuberculous patients treated with isoniazid for only a month.

From the experience reported above, it seems that marked decrease or reversion of tuberculin hypersensitivity is more likely in primary tuberculosis with a minimum of involvement, as shown by the absence of abnormal roentgenograms of the chest in the patients who did become skin-test negative to 1 mg. of old tuberculin.

Concern has been expressed[10] over the possibility that the specific acquired resistance against subsequent exogenous reinfection that is conferred by primary tuberculous infection may be lost as a result of therapy so effective as to cause complete loss of tuberculin hypersensitivity. It is well known that the tuberculin hypersensitivity and, probably, the specific acquired resistance conferred on human beings by BCG vaccination are by no means permanent. This fact per se is not considered a valid contraindication to BCG vaccination. By the same token the application of chemotherapy in primary, uncomplicated tuberculosis cannot justifiably be withheld, in spite of the possibility that such treatment will so successfully overcome the infection as to occasion complete loss of hypersensitivity and immu-

TABLE 3. *Patients with X-Ray Evidence of Tuberculosis without Reversion of Tuberculin Reaction on Isoniazid.**

PATIENT	AGE AT ONSET	PERIOD ON ISONIAZID AT LAST TUBERCULIN TEST
	mo.	mo.
J.J.†	8	12
D.W.†	5	17
W.T.†	6	16
G.W.†	9	11
J.A.†	12	8
V.A.†	5	7
M.H.†	4	7

*Dosage of 8 mg. per kilogram of body weight per day.
†Streptomycin received along with isoniazid treatment.

nity. Indeed it may be suggested that such persons, after such effective treatment, might be vaccinated with BCG. Or, if reinfection occurred, they could again be given chemotherapy.

Summary

Reversion of the tuberculin skin test in 4 infants treated with isoniazid for less than eight months is reported. This phenomenon had previously been observed only in laboratory animals.

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MEDICAL PROGRESS

CARCINOMA IN SITU*

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UNDER the term carcinoma in situ, Broders,[1] in 1932, described a group of lesions characterized by the appearance of certain abnormal types of cells within the normal confines of the epithelial layer. These cells manifest in appearance or in behavior various features that are characteristic of the cells of malignant tumors. They may entirely replace the normal epithelial cells over considerable distances, but they do not pass the barrier of the basement membrane and invade underlying tissues. The majority of these lesions were considered for many years to be "precancerous." Today, the preponderance of opinion is that they are a form or stage of actual cancer, as the name carcinoma in situ and its synonyms, intraepithelial and noninvasive cancer, indicate. Since there are no characteristic symptoms or physical findings, the diagnosis of carcinoma in situ is entirely a histologic problem; hence, the problem has entered the domain of the pathologist.

The development of exfoliative cytology made available a method for detecting cancer that had not yet become grossly evident. Thus, many asymptomatic lesions, especially of the uterine cervix, proved to be carcinoma in situ.

In an attempt to evaluate reports of carcinoma in situ, which have now been described in many different locations, it is immediately obvious that there is a wide variation in lesions so called. Poor photographic reproductions further handicap the critical reviewer. The difference between serial section, step section and the serial-block examination is not appreciated, and this is of vital importance when one is evaluating the presence or absence of carcinoma in situ after therapy because there is usually no grossly visible lesion.

Although Broders[1] deserves credit for emphasizing the importance and popularizing the concept of carcinoma in situ, one of the earliest and most lucid of the presentations that form the basis for present ideas on the subject is Schauenstein's[2] paper, published in 1908. He described 4 cases with similar epithelial abnormalities of the uterine cervix, 1 without invasion and the other 3 representing stages from minimal invasion to an advanced carcinoma. It was Rubin,[3] however, who first used the term carcinoma in situ in 1918, although he had described 2 similar cases in 1910.[4]

Since most of the reports in the literature pertain to lesions in the uterine cervix, it is appropriate that a large part of this progress report should be devoted to a consideration of the disease in this organ.

Uterine Cervix

As noted above, the earliest papers pertaining to carcinoma in situ dealt with its involvement of the uterine cervix, as have most reports since then. We have found well over 2500 cases reported as squamous-cell carcinoma in situ of the cervix. Most of these have appeared in the past decade. Although Schauenstein[2] and Rubin[3] described what they apparently considered noninvasive carcinoma, Schiller,[5] widely quoted, advocated the diagnosis of early cervical carcinoma, maintaining that carcinoma could be

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diagnosed without the presence of invasion. Later Smith and Pemberton[6] and Schiller[7] showed that this lesion might be followed by invasive carcinoma and considered that this sequence supported the idea that this was truly preinvasive carcinoma.

Since there are no gross or clinical features characteristic of carcinoma in situ,[8-11] exfoliative cytology has been responsible for the high prevalence of diagnosis of carcinoma in situ during the last decade.[12-14] Papanicolaou[15] pioneered the use of this method of detecting malignant lesions, and many laboratories now use his technic, his criteria and his terminology. Hundreds of reports of the use of cytology have appeared in the past eight years; many of them described patients who gave no clue to the presence of carcinoma but whose vaginal or cervical smears contained tumor cells and whose biopsies of benign appearing cervixes showed carcinoma in situ. For example, Nieburgs and Pund[16] studied cervical swabs from 10,000 patients, and of 185 histologically confirmed positive reports, 68 were preinvasive carcinoma. They further described specific cells with carcinoma in situ that were found in 71 smear preparations; 57 of these patients were proved to have carcinoma in situ, and 4 had invasive cancer. Reagan[17] also described the cell characteristic of carcinoma in situ but emphasized the fact that the same cell is seen in invasive squamous-cell carcinomas; these cells, therefore, should be recognized as neoplastic but are not pathognomonic of carcinoma in situ. The experienced cytologist should be as accurate in detecting carcinoma in situ as in detecting invasive carcinoma[18]; the smear will be positive even when only a small focus of tumor is present. However, the smear is only one diagnostic procedure and should always be confirmed by histologic examination before therapy is begun.

Microscopically, squamous-cell carcinoma in situ of the cervix bears only superficial resemblance to the normal stratified squamous epithelium. The loss of normal stratification is a constant and essential change. The presence of large nuclei high in the epithelium and the scant cytoplasm give a crowded appearance, and the normal picture of shrunken nuclei and abundant cytoplasm in the superficial cells is lacking. Nuclear changes are most striking: the chromatin pattern is coarse, and nuclei are large and vary in size and shape. Mitoses may be frequent and occur high in the epithelium. One pattern often seen is that of spindle-shaped cells that tend to be uniform in size and arrangement, but generally there is pleomorphism and irregularity of arrangement of cells. Epithelial pearls are rare in carcinoma in situ and when present should make one suspicious of invasive carcinoma.[19] There is very little or no glycogen in the cells in carcinoma in situ — hence, the positive Schiller test.

Schiller[20] described an oblique line that sharply delineated the normal epithelium from the carcinoma in situ. This line is formed by extension of the lesion under the normal epithelium as it grows. This feature is commonly seen, but its absence cannot be used as a criterion against the diagnosis. Gurski, Beaver and Nelson[21] found the "line" in only half their cases. Frequently, the transition from normal tissue to carcinoma in situ is gradual, taking place over a width of several millimeters or even several centimeters.

Involvement of endocervical glands is common. Reagan and Hicks[22] found it in 91 of 100 cases, Ulfelder[23] in 36 of 39 and Huey et al.[24] in 65 of 71. Younge, Hertig and Armstrong[25] and Pund and Blumberg[9] considered it a criterion of extensiveness of the disease and, therefore, of therapy. We have found involvement of the glands in such a high percentage of cases that we believe it is of doubtful value in this respect, especially if interpretations are made from biopsy specimens. In 1 case the only focus in a serially sectioned cervix was in a gland.[26] The Johns Hopkins group for many years believed that involvement of the endocervical glands indicated invasion,[27,28] but more recently they have reversed their stand.[29] We take strong exception to the conception of involvement of the glands as invasion. The lesion is still confined to a natural surface; so long as the growth is within the gland lumens and the lymphatic and blood vessels are not accessible, there is no danger of metastases. In a small group of cases studied for early invasion, invasion occurred as commonly from the surface as from the glands.[30]

Multiple independent foci of carcinoma in situ in the cervix have frequently been described. Although serial-block studies have disclosed two or more independent foci of carcinoma in as high as 50 per cent of one group studied,[31] Foote and Stewart,[32] in 27 cases studied by serial blocks, found two unconnected areas of tumor in only one specimen. Our experience approaches more closely that of Foote and Stewart; with the serial-block technic independent foci of tumor are uncommonly seen, and apparently separate foci are often found to be the extensions of serpiginous borders of carcinoma in situ when serial or step sections are examined.

The extent of the disease has been shown diagrammatically in papers by Foote and Stewart[32] and by Gusberg and Moore.[10] Although Foote and Stewart considered carcinoma in situ primarily a disease of the portio with secondary involvement of the endocervix, the large majority of reports indicate that it is primarily an endocervical disease with secondary portio involvement.[10,22,31,33] For example, in the last four reports cited, of 184 cases only 27 involved the portio. We agree with Pund and Blumberg[9] that carcinoma in situ should be thought of as an endocervical disease.

Carcinoma in situ may spread in all directions and yet may not become invasive. Frequently, the lesion completely encircles the cervix and extends up the

canal. It may even line the endometrial cavity and extend into the tubes and still remain intraepithelial.[34-37] The vagina may also be involved, and Wespi[38] described a case in which the carcinoma in situ lined the vagina. This extension may explain the occasional recurrence in the vaginal apex after hysterectomy[39,40] but is no indication of invasion or even imminence of invasion.

These data lead to the practical matter of deciding where to obtain the biopsy specimen. The report by Foote and Stewart[32] indicated that a one-point biopsy from the anterior or posterior lip would have detected the lesion in only 13 of the 27 patients; if two points, anterior and posterior, were biopsied, 20 would have been positive, and if four points were biopsied, 25 of 27 would have been found. Howard et al.,[33] in their study of 14 cases, stated that only two of the original single blocks taken from the extirpated cervix showed intraepithelial carcinoma. Pund and Blumberg[9] emphasized the value of endocervical curettage; in a series of 84 patients, curettings contained carcinoma in situ in 11 that would otherwise have been missed. Younge[41] made a plea for the use of the Schiller test to determine the proper site to biopsy, and for the biopsy to include both the squamous epithelium of the portio and the columnar epithelium of the endocervix.

Much emphasis has been placed on the value of cold-knife conization to obtain tissue for histologic examination.[24,42,45] The pathologist must examine this completely by multiple blocks, or there is no advantage over multiple-point biopsy. Novak[44] has spoken in favor of the "surface" biopsy, and it is true that the layer of carcinoma in situ often can be removed with ease; however, other biopsies that include subjacent stroma must then be done to rule out invasion before it can be assumed that the lesion is intraepithelial. The technic seems to have no real value. We believe that, before one can diagnose carcinoma in situ of the cervix, the minimum diagnostic procedures are biopsies that include the squamocolumnar junction at four different points around the cervix, and a curettage of the endocervical canal. It is essential to know first that carcinoma in situ is present and secondly that an invasive carcinoma is not present.

Histogenesis

Stoddard[19] accepted two types of origin for carcinoma in situ: one from portio epithelium usually at the margin of an endocervical ectopia, and the other from the endocervical subcylindrical basal cells or what are called reserve cells. Pund and Nieburgs[45] illustrated diagrammatically how they believe that the lesion develops from the reserve cells, either directly or by transformation to squamous-cell metaplasia and thence to carcinoma in situ. Meyer,[46] on the other hand, was strongly opposed to the concept of its origin from reserve cells. In our experience there has always been a connection with the squamocolumnar junction though apparent transformation from reserve cells can sometimes be seen.

Evidence of Progression to Invasive Carcinoma

It seems unquestionable that carcinoma in situ can progress to an invasive carcinoma. Younge et al.[28] deliberately followed a patient to establish the biologic potential of this histologic lesion; carcinoma developed in eleven months in the area of the original biopsy. Stoddard[19] accepted 42 cases as examples of progression to invasive carcinoma, but thought some of the cases were still in endocervical glands rather than truly invasive. The interval varied from ten months to thirty-seven years and averaged nine years. Kottmeier[47] accepted 46 cases and added 12 of his own. The exact number is immaterial, whether it is 50 or 100 cases or even 500; carcinoma in situ does progress to frank carcinoma, but the figure of 50 or 500 cases gives no clue to the frequency of this phenomenon. Of the thousands of cases of squamous-cell carcinoma reported in the past forty years, such a small number as 58 cases of carcinoma in situ with subsequent invasion should make one reluctant to make sweeping generalizations.

It is important to bear in mind certain points in analyzing past reports. In the first place clinically evident cervical cancer appearing a short time after a positive biopsy of carcinoma in situ probably means that the patient was inadequately studied; for example, Limburg's[36] 2 patients with cancer two and four months after the diagnosis of carcinoma in situ cannot be accepted. Secondly, the histologic changes should meet certain minimal criteria before being called carcinoma in situ if one is to evaluate its potentialities; the gradual transition from normal to atypical epithelium to classic carcinoma in situ can be seen in a single cervix or can be reconstructed by a collection of different specimens — where to draw the line is a most important and omnipresent question. Thirdly, invasive cancer may run a long course, and the report of Taylor and Guyer,[48] often cited as carcinoma in situ going on to invasive cancer, was shown to be invasive on further sectioning of the initial biopsy. Fourthly, the retrospective type of study,[49] confirming the progression to invasive cancer, does not take into account the fact that if carcinoma in situ does regress it would not be detected by that kind of review; the patients had cancer, or they would not have been so studied.

A small group of patients with proved carcinoma in situ received no treatment, and cancer did not develop. Stoddard[19] accepted 9 of these cases as bona-fide examples though 1 patient still had carcinoma in situ six years and eight months later. Of Petersen's[50] 54 cases 16 apparently regressed. Kottmeier's[47] series of 114 cases of carcinoma in situ, found by review of material at the Radiumhemmet in Stockholm, is very pertinent. Fifty-nine patients

received no treatment, and after five years 45 were free of clinical evidence of disease; 23 were alive and well after ten years. One of us (R.H.F.) has seen some of the slides from Kottmeier's laboratory showing typical carcinoma in situ. This gives a more encouraging outlook concerning the biology of the lesion even though in an unknown number of these cases invasive cancer may ultimately develop.

Attempts at statistical proof of the relation of carcinoma to invasive carcinoma have been made.[9,28,51] These have been principally based on a comparison of the "incidence" of carcinoma in situ to the "incidence" of invasive cancer, and on the fact that the difference in the average age of patients with both types is in the range of what has been found to be the latent period before carcinoma in situ becomes invasive. Superficially, this evidence seems convincing but Dunn[52] pointed out the fallacies in these conclusions. One of his important points concerns the misuse of the words "incidence" and "prevalence." He defines "incidence rate" for a disease as, "The rate of development of new cases of that disease in a defined population (usually one that is geographically circumscribed) in a designated time interval (such as year), expressed in some convenient population unit, such as per 1000 or per 100,000," whereas "prevalence rate" is "the proportion of a population having the disease at or in a specified time expressed in units of that population as just indicated." To illustrate his points Dunn arbitrarily assumed that all carcinoma in situ progresses to invasion and has a duration of five years and that the presymptomatic invasive carcinoma is of two years' duration. He showed by means of tables that after the first five years, the *prevalence* of carcinoma in situ was five times the *incidence* of symptomatic invasive cancer since all cases of carcinoma in situ accumulate as new tumors develop each year — that is, the cases in which carcinoma in situ has just developed, together with those in which it has been present one, two, three and four years, would all be found in a survey. The *incidence* could be determined by rescreening of the same population.

The evidence cited concerning the younger age of patients with carcinoma in situ is also refuted by Dunn. No significant data are available on the age-specific incidence or prevalence rates. Nieburgs[53] had some data on this matter, but these were not entirely free of selective factors. The discussion and accompanying table emphasized the impossibility of measuring the duration of carcinoma in situ from mean ages of the different groups.

Dunn[52] considered the fundamental questions to be, What percentage, if not all, of carcinomas in situ of the cervix are destined in time to become invasive? What percentage, if not all, of invasive cervical carcinomas begin as carcinoma in situ? What is the average duration of carcinoma in situ of the cervix, and how much time variation is there around this mean duration? It is hoped that answers will be forthcoming from the survey now being done in Memphis, Tennessee. Much can be learned from Dunn's paper. It is an important contribution.

Pregnancy and Carcinoma in Situ

Epperson et al.,[54] in 1951, reported 5 cases of carcinoma in situ of the cervix discovered during pregnancy, in which without treatment the cervix reverted to normal during post-partum follow-up study as determined by biopsies. Although the original diagnoses in these cases were confirmed by "well-known pathologists," their one photograph is not convincing. Nesbit and Hellman[55] added 2 cases. They expressed a reluctance to make the diagnosis of carcinoma in situ in pregnancy. Schleifstein[56] doubted the validity of the diagnosis in pregnancy, and Hertig[57] stated that he does not make the diagnosis of carcinoma in situ in a pregnant patient.

Conversely, Greene and his associates[58] and Peckham et al.[59] reported a total of 19 cases in which carcinoma in situ seen during pregnancy persisted. Only 3 of the cases, however, seem to be characteristic, the others demonstrating merely degrees of atypism in both ante-partum and post-partum specimens. Mullen and Foraker[60] reported a case with biopsies at the fifth and seventh months of pregnancy, a conization six weeks post partum, a biopsy at six months and a total hysterectomy at seven months. These tissues were studied by serial blocks and multiple sections. Slides were submitted to 5 different pathologists, all but 1 of whom agreed that carcinoma in situ was present in one or more biopsies and all of whom agreed that the hysterectomy specimen showed only basal-cell hyperactivity. Mullen and Foraker[60] suggested that the patients of Greene et al. were not followed long enough post partum for the lesion to regress as apparently happened in their case. In a superbly illustrated paper Hamperl, Kaufman and Ober[61] reported studies on the cervixes of 361 pregnant women and found 9 cases of carcinoma in situ or early invasive carcinoma, the latter of which they called "microcarcinoma." They concluded that the lesions do not regress so quickly, but expressed doubt that all progress to invasive cancer.

We believe that the histologic changes of carcinoma in situ, if seen during pregnancy, should be diagnosed as carcinoma in situ. If the lesion does regress it is further evidence of lack of knowledge concerning this lesion.

Treatment

Surveys conducted by Hoge,[62] who polled 70 leading gynecologists, indicated that treatment varied from conization, cervical amputation, vaginal hysterectomy, total hysterectomy with and without bilateral oöphorectomy, radiation and Wertheim's procedure, to radiation plus radical surgery. Many replies indicated that therapy varied with the age of the patient.

Carter et al.[63] gave the results of a questionnaire consisting of 6 problem cases with histologically proved carcinoma in situ in women ranging in age from twenty to sixty-two years. It was most heartening to see the large percentage of physicians who favored conservative management, with preservation of reproductive power in the younger women. With increasing age hysterectomy became the treatment of choice, and in older patients the tubes and ovaries were also removed.

Carter et al.[63] preferred operative treatment to radiation in all age groups. They favored vaginal hysterectomy, and did not consider that radical hysterectomy and radical pelvic lymphadenectomy were indicated for any patients with carcinoma in situ. Galvin and TeLinde[28] treated their patients with total hysterectomy and spared the ovaries; the hysterectomy was more extensive than the usual one, including more parametrial tissue and a 1-cm. vaginal cuff.

Younge[64] advocated conservative treatment especially in young women in the childbearing age. He cited 23 cases treated by conization, with no evidence of disease three to fourteen years later, and 6 others cured by biopsy as judged by negative serial sectioning of excised cervixes. Of 14 not cured by conization, subsequent hysterectomy did cure the patient though the operation was delayed as long as fourteen months. Carter et al. are following 21 of 126 gynecologic patients and 12 of 25 obstetric patients with no more active therapy than multiple-punch or cold-knife cone biopsies for diagnostic purposes.

In more recent reports a tendency away from radical therapeutic measures is evident. This seems to be the obvious approach as more is learned of the slow progression, and possible regression, of this lesion and it is appreciated that simple procedures may be curative. For example, among the cases reviewed by us in the literature, there were 115 hysterectomy specimens in which no carcinoma in situ was found after biopsy alone (not conization); some of these specimens were examined by serial section. At the Massachusetts General Hospital a small group of patients with proved carcinoma in situ are being followed closely without treatment; vaginal smears and biopsies are taken periodically, and some smears have become negative.

(To be concluded)

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MEDICAL INTELLIGENCE

DISAPPEARANCE OF DIABETES INSIPIDUS AFTER PROGRESSIVE AND COMPLETE DESTRUCTION OF THE PITUITARY GLAND BY METASTATIC CARCINOMA*

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METASTATIC tumors in the brain occur in approximately 5 per cent of all fatal cases of cancer, according to Willis.[1] A survey of 3946 consecutive autopsies by Earle[2] suggests that metastatic brain tumors are more common than primary intracranial tumors in the adult male.

Metastatic lesions of the pituitary gland are most uncommon but are not considered rare, for the medical literature is well documented with isolated cases over the past thirty-eight years. In Willis's series the most common source was primary carcinoma of the breast, the lung being second in frequency. In many cases, as in the one reported below, the primary carcinoma of the lung is unsuspected clinically, and the metastasis to the brain produces the main clinical picture. Almost always the metastatic growths in the pituitary gland recorded in the literature occupy the posterior lobe; metastases in the anterior lobe are exceedingly rare.[1-3] In many cases, as the posterior pituitary gland is destroyed by the invading tumor, symptoms of disturbed pituitary function take the form of diabetes insipidus with polyuria and excessive thirst, but a functioning anterior pituitary lobe must be present.[4-8] Several clinicians and investigators have advanced the theory that, with extension of the tumor from the posterior to the anterior lobe, the diabetes insipidus will disappear.[9-12] Three of them stated that this had been observed clinically, but failed to refer to specific cases.[9,12,13] Actual case histories demonstrating this phenomenon are extremely rare; in fact, we were able to locate only 1 in the medical literature in the past thirty-eight years, this being the case of Simmonds[11] reported in 1914 and later referred to by Piney and Coates[10] in 1924. In the case presented below this unusual and rare clinicopathological finding was also present.

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Case Report

W.H., a 69-year-old retired businessman, was admitted to the Richmond Eye, Ear, Nose and Throat Hospital on May 27, 1953, with the chief complaints of bilateral blindness, anorexia and generalized weakness.

The eyes had been examined for a number of years by an ophthalmologist, and in 1947, both eyes showed 20/20 visual acuity. On January 26, 1952, he was seen at his home complaining of generalized weakness and lack of energy; he was voiding at frequent intervals during the day, and hourly nocturia was present. The urine contained no sugar. On January 29 the diagnosis of diabetes insipidus was made, and he was given an ampoule of Pitressin daily, by intramuscular injection, for 3 days. The polyuria greatly decreased under this therapy. The drug was discontinued for the next 5 days, when symptoms recurred; the diagnosis of diabetes insipidus was established. Pitressin in oil was started on February 5 and was continued on a schedule of 1 ampoule every other day until March 14. He then refused to take the drug, which he thought was making him more depressed and weak. This was followed by a relapse, but no further medication was given until March 24, when both visual fields appeared to be entirely normal. Vision was 20/20 in the right and 20/30 in the left eye. The only abnormality noted was that the left pupil was slightly larger than the right. On March 25 x-ray examination revealed a skull of normal general appearance. The position of the pineal body tended to exclude a pineal tumor. There was evidence of osteoporosis in the pituitary fossa, whose contour, however, was reasonably preserved, and the change was not sufficient to suggest a positive diagnosis of pituitary tumor.

On April 7 the patient complained of being very weak and the polyuria had returned to some degree, no Pitressin having been taken for 2 weeks; however, the polyuria was not as severe as when it was first noticed in January. He refused to enter a hospital for further studies and treatment. He was seen, thereafter, at irregular intervals at his home. No further Pitressin was given after the last injection on March 24, but the polyuria gradually disappeared and never returned.

On 2 occasions in April, the specific gravity of the urine was recorded at 1.012 and 1.018. In February, 1953, the patient first began to notice a gradual loss of vision of the left eye. He was advised to have his eyes rechecked but failed to do so until April 24, when the vision in his right eye was recorded as 20/25, and that in the left as less than

10/200. There was moderate sclerosis of the retinal arteries and the blind spot on the left side was increased in size. With glasses, the right eye was corrected to 20/20. At the time of admission to the hospital, there was complete loss of vision in both eyes except for detection of strong light. He further complained of increasing weakness, especially in the past month, and he had to be assisted when he walked. There had been a weight loss of approximately 4.5 kg. in the past 6 months.

A diagnosis of duodenal ulcer was established by x-ray examination in 1926. The patient was treated with symptomatic therapy and had remissions and exacerbations throughout the next 20 years. He had repeated x-ray studies during this time, the last (in April, 1946) showing extensive scarring of the duodenum but no obstruction. Since that time, he had had relatively little trouble with his ulcer. In September, 1949, he was given electric-shock treatments for involutional melancholia; however, he failed to show much improvement. In April, 1951, a polyp was removed from the rectum, with the pathological diagnosis of Grade 1 adenocarcinoma, without invasion of the polyp's stalk. In the following June he was treated in a mental institution for anxiety neurosis, depression type.

Physical examination showed a somewhat confused and drowsy man; it was impossible to get a detailed history from him. He was apathetic and thin, almost to the point of cachexia. The positive findings were limited to the eyes, in which there was complete loss of vision except for light perception. The pupils were fixed to light. The optic disks were well outlined, and the retina was pale, with a moderate amount of sclerosis. A complete neurologic examination failed to reveal any further positive findings.

The temperature was 98.6°F., the pulse 78, and the respirations 18. The blood pressure was 110/70.

The hemoglobin, white-cell count, fasting blood sugar and nonprotein nitrogen were normal. The blood Wassermann reaction and urinalysis were negative. The cerebrospinal fluid revealed a normal cell count and protein content. An electrocardiogram presented a definitely abnormal record, with an atrioventricular block and a QRS interval of 0.10 seconds. An x-ray film of the chest showed healed fibroid tuberculosis, with apical pleural thickening and calcification in the right upper lobe and in the apex of the left upper lobe and a few calcifications in the lower lobe. The heart was small, and the aorta arteriosclerotic. X-ray studies of the skull suggested erosion in the posterior and anterior clinoid processes of the sella turcica. There was slight calcification 2 cm. above the sella. Definite pathologic change was suggested, with the possibility of tumor or tuberculoma in the region of the hypothalamus. X-ray films of the frontal and ethmoid sinuses were clear. An encephalogram on June 2, for which 50 cc. of air was used, showed a suspicious lesion above and just posterior to the sella, suggesting the possibility of an aneurysm or a malignant type of basilar intracranial tumor.

The night after the encephalogram was taken the patient went into a state of collapse, the blood pressure falling to 40 systolic; however, this gradually improved over the next 12 hours and was followed by a gradual rise in temperature to 102.5°F. on June 3. He gradually failed, and died on June 7.

At autopsy, the sella turcica was widened and deepened to a diameter of 3 cm. There was slight erosion of the posterior clinoid processes. The sella was occupied by a tumor mass, 3 cm. in diameter, that pressed on the optic chiasm, the optic nerves and the hypothalamic region. There was invasion of the right optic tract. The tumor was firm and pale and, on section, contained a cyst, 5 mm. in diameter, filled with dark-brown fluid. Histologic examination of the tumor showed a carcinoma with poorly differentiated epidermoid characteristics. A thin rim of compressed anterior-pituitary tissue was seen in the anterior portion of the tumor. The findings suggested that the metastatic lesion had first completely destroyed the posterior lobe and then advanced into the anterior lobe. No bony invasion was noted.

On dissection of the lungs a tumor, 5 cm. in diameter, was found in the wall of the superior-segment bronchus of the left lower lobe. There were metastases to the regional lymph nodes. Histological study revealed epidermoid carcinoma morphologically similar to that in the pituitary gland that was undoubtedly the primary neoplasm.

Additional findings comprised generalized arteriosclerosis, scattered petechial hemorrhages in the brain, bilateral healed apical tuberculosis and passive congestion of the viscera. The final anatomic diagnoses were carcinoma, epidermoid type, of the superior-segment bronchus, left lower lobe, with metastases to the hilar lymph nodes and pituitary gland and subsequent destruction of the pituitary gland; emphysema of the lungs; anthracosis of the lungs; healed tuberculosis, right and left apexes of the lungs; healed pleuritis on the left; arteriosclerosis, generalized, moderate; and congestion of the lungs, liver, spleen and kidneys.

Discussion

The mechanism of diabetes insipidus is not completely understood although an impressive amount of work has been done and much has been written about the subject. The secretion of the antidiuretic hormone of the posterior lobe of the pituitary gland varies continually with the current osmotic pressure of the arterial plasma.[14] The production of the hormone is regulated by the nerve supply of the posterior lobe, which originates, for the greater part, in the supraoptic nucleus of the hypothalamus and passes down the pituitary stalk to the lobe.[15] By acting directly on the kidney tubules the antidiuretic hormone facilitates the reabsorption of water. Deficiency of this hormone will cause polyuria and diabetes insipidus only if the anterior lobe of the pituitary gland remains intact. Therefore, diabetes insipidus will result by interference at any level with the functional integrity of the system outlined.

The role of the anterior lobe in this symptom complex is poorly understood. It is generally agreed that the endocrine regulation of water metabolism assigns some diuretic role to the anterior pituitary lobe by its stimulating effects on the adrenal cortex and by direct action on the renal function. Therefore, it is concluded that, in the regulation of water metabolism, the hormones of the anterior and posterior lobes of the pituitary gland and the adrenal cortex constitute an interacting system.[4]

In 1914 Simmonds[11] observed a case in which a primary carcinoma of the mammary gland had given rise to a metastasis in the posterior lobe of the pituitary gland. Nine months before death, there was polyuria, which disappeared after a few weeks. At death the anterior pituitary lobe was extensively invaded by the tumor.[10,11] As mentioned above, this was the only other case that we could find in which the diabetes insipidus disappeared after invasion of the anterior lobe as proved by autopsy. Several factors may account for this rare observation. With an enlarging malignant growth, the interval between onset of the diabetes insipidus and death is usually short, — only a few weeks or month, — and little time is thus allowed to prove this theory by the intermittent use of Pitressin. In a case reported by Norman and Silliphant[16] the polyuria developed a few months before death and was controlled by the use of Pitressin. At autopsy the entire pituitary gland was involved. It is possible that if the Pitressin had been discontin-

ued in that case a few weeks before death, the polyuria might not have been present at that time, since the anterior lobe was also involved, as proved at autopsy.

It has been stated that complete hypophysectomy has never been known to produce diabetes insipidus.[7] On the other hand Heinbecker and White[17] have been unable to improve the polyuria in dogs, produced by complete removal of the entire neurohypophysis of the posterior pituitary lobe, by subsequent or simultaneous removal of the anterior pituitary lobe. Thus, the exact role of the anterior pituitary gland in water metabolism is not completely understood, and further clinical and experimental study will have to be carried out before the entire picture is clear.

It should be emphasized, from the neurosurgical standpoint, that even though x-ray examination of the chest before operation was negative, a bronchogenic carcinoma was found at autopsy. This is not an unusual clinical experience. Furthermore, the patient's age and generalized debility completely ruled out any surgical exploration, since he had Simmonds's disease with the other pituitary disturbances.

Summary

A case is presented in which diabetes insipidus developed as the result of a metastatic carcinomatous lesion from the lung to the posterior lobe of the pituitary gland. As the tumor later involved the anterior lobe, the diabetes insipidus disappeared. The mechanism of diabetes insipidus in this rare clinical observation is discussed.

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IRIDECTOMY — A CENTURY OF PROGRESS

Hedwige Habegger, M.D.*

BOSTON

WITHOUT doubt the middle of the nineteenth century was the golden age for ophthalmology, which suddenly arose as a science out of the discovery of a means of examining the inner eye. The invention of the ophthalmoscope by Hermann Ludwig Ferdinand von Helmholtz in 1851 paved the way for a succession of new and more refined methods of diagnosis and treatment — especially of glaucoma.

Among the brilliant workers of the period who made fundamental contributions to an understanding of glaucoma was Albrecht von Graefe, who demonstrated, in the period 1855-1860, the value of iridectomy in relieving raised tension in the hard, glaucomatous eye. The figure of this first German professor of ophthalmology stands out because he had vision enough to apply the new methods of examination clinically and was thus able to reason from his observations more profoundly and to greater purpose than other clinicians of his time. From his investigations he laid the foundations of both a scientific and an applied ophthalmology.[1] He was the first to apply to their full extent the principles of focal illumination in the clinical examination of the outer eye and funduscopy for exploring and interpreting the microcosm within. He was among the earliest exponents of transillumination for the detection of tumors, the first to interest himself in, and to apply, the results of measuring the tension of the eyeball by instrumental tonometry and the first to take clinical records of the pathologic visual field. Apart from these pioneer activities there is hardly an aspect of clinical ophthalmology upon which he has not left his mark, and he has left behind him two monuments, which have grown in magnitude with the passing years: the *Heidelberger Ophthalmologen Gesellschaft* (1857) and the *Archiv für Ophthalmologie* (1854).

In that journal he[2,3] described in a masterly way the symptoms of the congested glaucomatous eye, the hardness of the eyeball, the wide, dilated pupil, the anesthesia of the cornea, the low anterior chamber, the vascular changes in the subconjunctival veins, the venous and arterial pulse in the retinal vessels, the extravasation in the choroid and retina and the increasing cupping of the optic nerve. In dramatic terms he related the history of a man of fifty complaining of "light flashes," "fireballs" and great pain in his forehead, who could hardly see the movement of the examiner's hand in front of his eyes. Having ascertained the existence of acute glaucoma with its bad prognosis and having tried the usual treatment Graefe came to the conclusion that "in a disease

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which constantly despises therapy a new measure should be applied." "Numerous sad experiences in the past," he added, "gave me the courage to undertake with this patient another treatment, and I went ahead to perform paracentesis of the anterior chamber; after the aqueous humor escaped, the iris and pupil were much clearer."

This original and ingenious idea revolutionized treatment, and the procedure is still valuable today in acute congestive glaucoma. Graefe taught that the sooner iridectomy is performed, the better the results, and that the incision should be as eccentric as possible, to remove the iris as far as its ciliary attachment. The more intense the symptoms, the more extensive the incision, he advocated, and aqueous should escape slowly. A year and a half's experience permitted him to write: "I believe that iridectomy is of real benefit in the glaucomatous process, but it has its limits of indications as has every other surgical method." This work anticipated the necessity for a filtering scar and inspired the effort of his pupil, Wecker,[4] who undertook to find a method whereby permanent filtration of the intraocular fluid could be established through the coats of the eye. Wecker strenuously fought a rising tide of opposition, which at one time threatened his master's classic method of basal iridectomy, in a lengthy monograph that remains a major contribution to the treatment of glaucoma.

Another distinguished surgeon, Jacques Daviel, performed iridectomy in some cases in the course of the first operations designed to extract a cataract. In a letter to the celebrated Haller, dated September 30, 1761, he wrote as follows[5]:

> I took away one half of this membrane (the iris) in order to form an artificial pupil since the natural one had been almost entirely destroyed. This is not the only time that I have been obliged to take away the iris or to make a section of it, and without having seen the least accident follow. I have some great observations to give on this subject . . . [unfortunately, Daviel died in 1762 before publishing them].

The honor of having successfully performed cataract extraction after preliminary iridectomy belongs to Mooren (1864),[6] but it was Graefe who introduced the combined modified linear operation (1865), reducing infection after cataract extraction from 10 to between 5 and 2 per cent. This alone was reason enough for widespread acceptance.

As for the place of iridectomy in the therapy of glaucoma, its merits and demerits have been debated by ophthalmologists for years, but Graefe's procedure has survived a full century as the preferred treatment of acute congestive glaucoma.

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Correction: The first footnote on page 860 of the Medical Progress report, "Application of Homeostatic Principles to the Practice of Parenteral Fluid Therapy," by Talbot et al. in the May 19 issue of the *Journal* should be changed to read, "A liter of this solution can be prepared by mixture of 30 ml. of 5 per cent dextrose in saline and 220 ml. of 5 per cent dextrose in water."

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41231

PRESENTATION OF CASE

First admission. A sixty-year-old jeweler entered the hospital for evaluation of a gastric condition.

For about ten years he had been having epigastric distress that responded to bland diets and antacids. Six years before admission he had an episode of hematemesis, and an x-ray film of the stomach was said to have shown an ulcer. He was treated conservatively but continued to have discomfort. There had been no melena or hematemesis since that time.

The past history revealed sinus trouble and a postnasal drip for years.

Physical examination showed a dark man of slender build. Tonsillar tissue was present but without any enlargement. There were a few enlarged, soft supraclavicular lymph nodes on the left side. The heart was normal. There were definite musical, coarse rales at the right apex after coughing, but no dullness or bronchial breathing. The liver was not palpable. A questionable mass was palpated in the epigastrium. Rectal examination was negative. Reflexes were sluggish but equal.

The temperature was 97.3°F., the pulse 72, and the respirations 18. The blood pressure was 118 systolic, 70 diastolic.

Urinalysis and examination of the blood were negative. A gastric analysis showed free hydrochloric acid and a +++ guaiac test. Two stool specimens were guaiac positive, but two subsequent specimens were negative. An x-ray film of the chest demonstrated bilateral thickening of the apical pleura and prominent markings in the upper-lung field. No hilar lymph nodes or calcification was seen. An x-ray film of the stomach revealed a tremendous increase in the size of the mucosal folds and stippling along the lower portion of the lesser curvature suggestive of shallow ulcers (Fig. 1). An acute ulcer at the angulus and extensive superficial acute gastritis were found on gastroscopy. The patient was treated symptomatically and was discharged after eighteen days.

Second admission (two months later) for gastroscopy, which revealed healing of the previously described ulcer, with evidence of slight to moderate gastritis.

Third admission (six months later) for another gastroscopy, which showed severe acute superficial gastritis. An x-ray film of the chest at this time disclosed a low diaphragm with limited respiratory movements. The lung markings were prominent, and the hilar shadows were increased. The folds of the stomach were absent in an area about 4 cm. in diameter along the lesser curvature just above the midportion.

Fourth admission (one year later). In the interval the patient continued to have the same epigastric discomfort and had had a few colds. He was admitted to the hospital for surgical evaluation.

The physical findings were unchanged except for a few more palpable cervical and inguinal lymph nodes and emphysematous moist musical rales throughout the chest.

Urinalysis was negative. The white-cell count was 14,600, with 49 per cent neutrophils, 25 per cent lymphocytes, 18 per cent monocytes, 3 per cent eosinophils, 3 per cent basophils and 2 per cent blasts. Red cells, platelets, hemoglobin and sedimentation rate were normal. A barium-meal examination was similar to the previous one.

A gastroscopy showed acute and subacute superficial gastritis. A piece taken for biopsy from the cardia demonstrated normal esophageal mucosa beneath which was a dense infiltration with normal-appearing mature lymphocytes. A very mature form of malignant lymphoma could not be excluded. Because of the patient's pulmonary condition a laparotomy was not performed; he was given a total of 600 r to the stomach and was discharged after two weeks.

Fifth admission (seven weeks later). Since discharge his condition had been unchanged except for an increase in severity of the epigastric discomfort and chronic cough.

Physical examination was unchanged. The temperature, pulse, respiration and blood pressure were normal.

Urinalysis, blood count and differential, hemoglobin, blood chloride, total protein and nonprotein nitrogen were within normal limits.

A laparotomy was performed the day after admission. The operative note was as follows:

> The lateral portion of the stomach was normal in appearance. The liver was smooth and normal. As one approached the esophageal hiatus it was first noted that the stomach became more and more thickened. The gastrohepatic omentum was a little edematous and pale, and farther up the stomach the serosal layer was granular and frosted in appearance. On palpation there was a definite suggestion of a mass in relation to the greater curvature very high up. When this area was brought into view, it

was noted that this represented merely an accentuation along the greater curvature of the process already described. The gastrocolic omentum was normal in appearance. As one went up the greater curvature it was noted that it at first became slightly pink and then edematous and pale. High up, a small segment of omental tissue was definitely adherent to the greater curvature of the stomach by what appeared to be inflammatory adhesions. A small area on the serosal layer of the stomach, not over 3 cm. in diameter, was removed for pathological examination. A mass that was taken to be an ectopic left kidney proved to be a mass of the midtransverse colon, which was characterized by a fleshy, pink growth of tissue extending from the mesenteric border on each side, upward and around and almost meeting in the midline on the antimesenteric side. The lumen of the colon was encroached upon, but apparently by pressure from without. This mass was about 7 cm. in length and possibly 6 cm. in width. There were a number of firm glands near by. No other gross disease was noted except that the spleen was probably twice the normal size. A piece of the lesion from the transverse colon was removed for pathological examination.

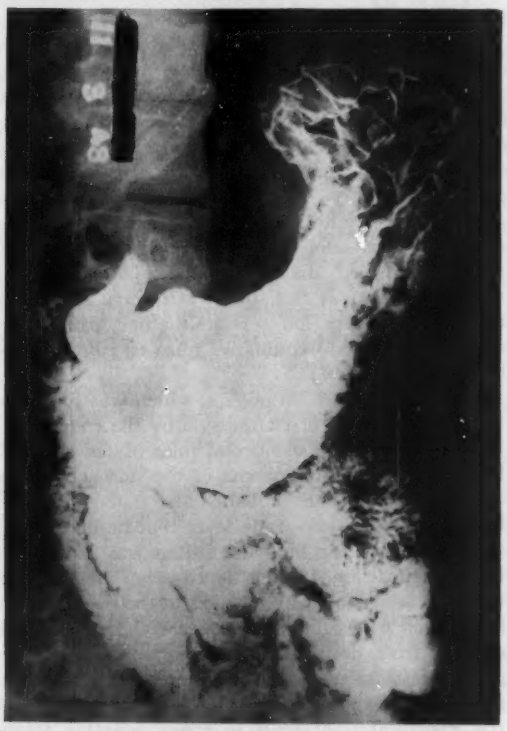

FIGURE 1. *Right Anterior Oblique View of the Barium-Filled Stomach before Irradiation, Showing Extreme Thickening of the Folds in Its Proximal Half.*

The biopsies from the stomach and colon were reported as showing malignant lymphoma. Five days postoperatively x-ray treatment with the 1,000,000-volt machine was begun. A total of 1500 r over a fifteen-day period was delivered to the abdomen over a 20-by-30-cm. portal area. The patient was discharged after a month in the hospital.

Sixth admission (three years and ten months later). In the intervening years the epigastric symptoms had abated. X-ray studies of the stomach showed gradual lessening of the mucosal thickening. However, chest films demonstrated an increase in linear and nodular densities throughout both lung fields more prominent on the right and chiefly in the upper-lung field (Fig. 2). For the past five years the patient had also noticed increasing exertional dyspnea accompanied by chronic cough. He had had more "colds" each year, and his cough was occasionally productive of blood-flecked sputum. One or two weeks before admission mild fever developed. There had been no orthopnea or paroxysmal nocturnal dyspnea. He had had a feeling of distention and had lost some weight in the past few months.

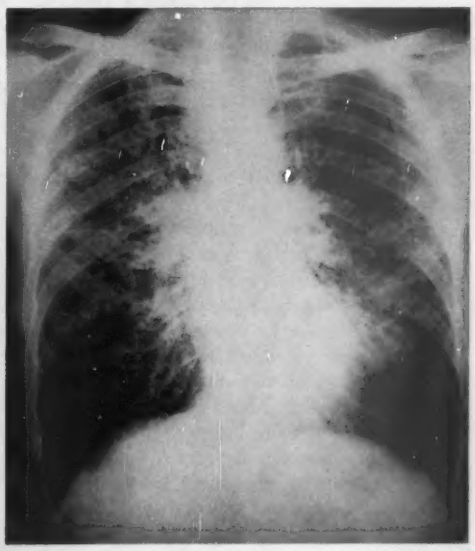

FIGURE 2. *Posteroanterior Roentgenogram of the Chest, Taken Three Years and Ten Months after Laparotomy, Showing Diffuse Granular and Nodular Lesions in Both Lungs, with Prominent Lung Roots Bilaterally.*

Physical examination revealed a chronically ill man. There were shotty lymph nodes in the left supraclavicular area besides those already noted in the previous admission. The excursion of the diaphragm was limited. Decreased breath sounds, coarse rhonchi and harsh and musical rales were heard all over the lung fields. The remainder of the physical examination was negative.

Urinalysis showed a + test for albumin. The white-cell count and differential, hemoglobin and red-cell count were normal. Vital-capacity determinations were 53 per cent (2.4 liters) and 62 per cent (2.8 liters). A smear of the sputum was negative for acid-fast organisms.

The patient ran a normal temperature curve. He was treated with nitrogen mustard for a total of 39 mg. in six days. He was discharged after fifteen days.

Seventh admission (six weeks later). He was admitted to the hospital for further therapy. He had had nausea, weakness, cough and epigastric discomfort, but had also gained some weight since discharge.

Except for a palpable liver and a slightly palpable

spleen, physical examination was unchanged. Outwardly, he appeared improved. Urinalysis was negative, and cell counts, differential and hemoglobin were normal. He was given two doses of nitrogen mustard at 12 mg. each and was discharged after four days.

Eighth admission (four months later). The exertional dyspnea had become increasingly severe, and an x-ray film of the chest had shown accentuation of pulmonary densities (Fig. 3).

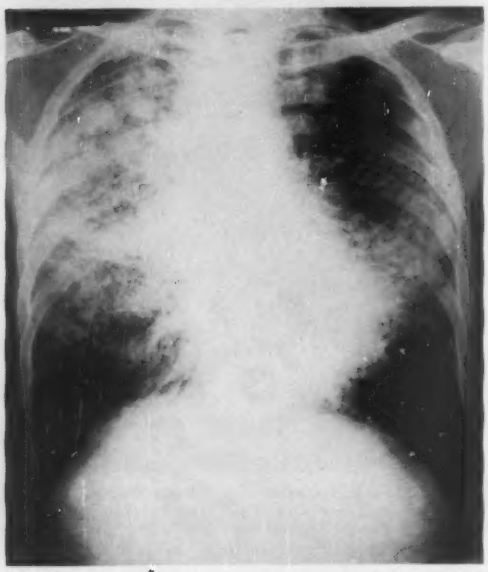

FIGURE 3. *Posteroanterior Roentgenogram of the Chest Six Months Later, Showing Progression of the Pulmonary Lesions, with Conglomerate Areas of Density in the Upper Half of the Right Lung.*

Physical findings were unchanged except for thickened lymphoid tissue in the pharynx. There were no significant changes in the laboratory examinations except for two white-cell counts of 4300 and 3400 and differentials of 83 per cent neutrophils, 7 per cent lymphocytes, 7 per cent monocytes and 3 per cent eosinophils and 75 per cent neutrophils, 17 per cent lymphocytes, 5 per cent monocytes, 2 per cent eosinophils and 1 per cent young neutrophils respectively.

The patient had occasional low-grade rises in temperature and one episode of diarrhea. A total of 900 r was delivered to each of the anterior and posterior sides of the chest, and he was discharged subjectively improved after two weeks.

Final admission (six months later). He had continued to be dyspneic with paroxysms of cough that sometimes improved with chlortetracycline (Aureomycin). He had had two episodes of hemoptysis since the last admission. New findings on physical examination included dullness over both lung fields posteriorly, a prolonged expiratory phase and splitting of the second heart sound.

Routine laboratory examinations were unchanged.

Low-grade rises in temperature, tightness of the chest and a choking sensation developed. He was treated with cortisone and placed under oxygen. He was discharged after ten days.

Course outside hospital. The patient steadily failed, with increasing respiratory difficulty and discomfort. He died fourteen months after discharge.

DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB*: Very few chemical determinations were done on this patient during his many admissions. To ascertain whether severe emphysema was present, I should like to know the carbon dioxide combining power and the chloride content of the plasma.

DR. BENJAMIN CASTLEMAN: Those determinations were not done.

DR. AUB: During the eighth admission the white-cell count was low, and the percentage of lymphocytes was low; that sometimes happens late in lymphoma. The high eosinophil count is also consistent with lymphoma. The patient had received a very large dose of nitrogen mustard a little over five months previously — more than enough for an obese patient, and yet he was described as being thin — and six weeks later was given another 24 mg. of nitrogen mustard. In spite of these large doses the white-cell count at this time was normal, and since this is too long a period to relate the mustard therapy with the low blood counts we must ascribe them to his disease.

This patient had lymphoma, which was suggested at the time of the first admission by the tremendous increase in size of the mucosal folds of the stomach. He obviously had lymphoma of the stomach and of the large bowel and probably also had generalized lymphoma. The low-grade fever that he had during the eighth and the final admissions was probably a Pel–Ebstein fever. During the fourteen months after the final admission, any changes in the disease could have taken place, for such a disease characteristically changes from day to day. Since the disease in the gastrointestinal tract was diagnosed, and since the symptoms changed from those mainly pointing to the gastrointestinal tract to those referable to the lungs, I suppose that is the problem I am expected to discuss.

Before I see the x-ray films, which should help a great deal, I should like to discuss the lesions in the lungs. The differential diagnosis I should say lies among lymphoma, bronchiectasis and possibly tuberculosis, although I believe the last is unlikely. The patient had sinusitis and a postnasal drip. There is a great difference of opinion about the relation of postnasal drip to bronchiectasis. Dr. Donald S. King does not believe that postnasal drip has anything to do with bronchiectasis. The physicians in some clinics in Switzerland consider bronchiectasis to be con-

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genital. I believe that postnasal drip that continuously bombards the lungs diffusely with infected material is a source of bronchiectasis. The patient gradually became a pulmonary invalid, with hemoptysis, which is consistent with bronchiectasis. As a matter of fact, although the history did not suggest it, he apparently was a pulmonary invalid at the time of the first admission, for the surgeons would not operate on him to treat the disease noted in the stomach. Against bronchiectasis is the evidence that the lesions began at the right apex. The pleural thickening would fit with either lymphoma or tuberculosis. The hilar markings described might be seen with either lymphoma or bronchiectasis. Lymphoma occasionally produces nodular lesions in the lungs that are difficult to distinguish from bronchiectatic lesions. The pulmonary densities could not be interpreted as pulmonary fibrosis from x-ray therapy, for they were present and had become accentuated before he received x-ray therapy to the chest.

The patient became a more and more chronic invalid and died with pulmonary insufficiency and probably right-sided cardiac failure as well.

May I see the x-ray films?

DR. C. C. WANG: On the films of the stomach taken nine years before the final admission one can see tremendous thickening and widening of the mucosal folds in the proximal half of the stomach (Fig. 1); the small bowel shows no significant abnormalities. At that time, however, the diagnosis of gastric lymphoma was made. Gastrointestinal series taken five and seven years later, after x-ray treatment to the stomach, demonstrate considerable diminution in the size of the gastric folds, but the folds along the greater curvature remain fairly prominent. The chest films taken on the first admission were considered normal at that time. Three years later, for the first time, there is an increase in the prominence of the pulmonary markings, with a stippled appearance of the peripheral lung fields.

DR. AUB: Was the diagnosis of lymphoma of the stomach made nine years previously?

DR. WANG: Yes; it was. The film of the chest taken two years after the last set shows no significant change except for greater prominence of the hilar shadows (Fig. 2). A year later there has been marked progression of the pulmonary changes, consisting of a miliary process throughout the lung fields; the bases of both lungs are fairly clear. There is some degree of pulmonary emphysema. The hilar lymph nodes are probably enlarged. The heart shadow is not unusual. Two years before the patient's death, there is further progression of the pulmonary process and a conglomeration of the nodular densities in both lung fields, particularly pronounced in the right upper lobe (Fig. 3).

DR. AUB: What happened after the chest was irradiated?

DR. WANG: There was no significant improvement after x-ray therapy.

DR. AUB: This is the most peculiar x-ray film of the chest that I have ever seen. It is not due to coccidioidomycosis.

DR. WANG: I do not see any evidence of bronchiectasis.

DR. AUB: I also think that bronchiectasis has been eliminated. I cannot make any diagnosis except that this man had a very unusual chest, possibly from malignant lymphoma in its late stages, when it does not respond to x-ray therapy. I do not know what else to say. I think it fantastic that a man could live two years with lungs that look like that on x-ray study.

DR. WALTER BAUER: This man had extensive pulmonary disease and yet lived for two more years. It is for this reason that I seriously question lymphoma of the lungs. I do not know what disease he had. I suggest sarcoidosis even though the x-ray picture is unusual. I do not believe that he died of lymphoma of the lungs; I do not think you do either.

DR. AUB: I do not know what to call it.

DR. BAUER: I do not know whether or not this was a yeast infection, which evidently was never entertained very seriously. I think sarcoidosis is as good a guess as any; however, I do not remember ever seeing such large parenchymal lesions in sarcoidosis. In periarteritis nodosa multiple parenchymal nodules simulating either miliary tuberculosis or lymphoma can occur.

DR. CASTLEMAN: Yeast infections have occurred with lymphoma quite often, but usually there is cavitation; there was no cavitation here.

DR. EDWARD B. BENEDICT: Was there an old suppuration at the base, which broke down with the x-ray therapy?

DR. AUB: One film was taken before any x-ray therapy was given to the chest.

DR. EARLE M. CHAPMAN: I should like to ask Dr. Kranes if he considers that this type of spread to the lung may have been from a primary carcinoma of the pancreas.

DR. ALFRED KRANES: Since the patient lived this long, I should reason, as Dr. Bauer does, that the pulmonary lesions were not due to a malignant process.

DR. JACOB LERMAN: In the days when tuberculosis was common its association with lymphoma was frequent, but now that tuberculosis is less common, we do not see this combination so often.

DR. BAUER: I doubt if he would have lived two more years if these changes had been due to tuberculosis. I think it must have been a benign process like sarcoidosis.

DR. CASTLEMAN: I agree with Dr. Bauer that it would be unusual for a patient with such a severe lymphomatous process to live for three years.

Should you like to comment, Dr. Aub, on the fact that he had lymphoma for nine years with little change?

DR. AUB: I do not think that is so surprising; he

probably had lymphoma for eighteen years, beginning when he was fifty; starting late, the disease may have given rise to a longer course. The pathologist evidently considered it a benign form of lymphoma; the cells were small and tightly packed. If he did not acquire an infection, I should say that he could have lived for two years with the lung lesion, which he apparently did. I suppose he became an invalid.

DR. CHAPMAN: I should like to ask a question about the 1500 r to the abdomen. Recently, I wanted to treat a patient with 700 r and was told that that much treatment was very dangerous to the intestinal canal. What is your opinion about that much x-ray therapy to the abdomen? Is there much of a reaction in the normal gut?

DR. AUB: That depends on how fast the treatment is given. Lymphomatous lesions usually do not have many ulcerations and are predominantly submucosal; therefore, I should not worry about a reaction in them. About its effect on the normal intestinal mucosa, the intestinal mucosa cells divide very rapidly, being quite similar in this respect to bone marrow. Any cells that are dividing rapidly are more sensitive to irradiation. One might, with too much x-ray therapy, denude the mucous membrane of the normal intestinal tract. I do not think the 1500 r would scare me; would it you, Dr. Wang?

DR. WANG: No; normal small intestine can take 4000 to 4500 r in a period of four to six weeks.

DR. CHAPMAN: As much as 4000 r in four weeks without upsetting the intestinal tract!

DR. WANG: A patient who received that amount of radiation would have suffered some diarrhea, but no permanent damage.

DR. CASTLEMAN: Dr. Pittman, do you have a comment?

DR. HELEN S. PITTMAN: I should put a small bet on lymphoma. My second choice would be fibrosis, which is just another way of saying that I have no idea what it was.

DR. STANLEY M. WYMAN: When I saw this patient for examination of the stomach, at the time of the seventh admission, the changes in the lungs during the preceding year impressed us greatly. We thought, as Dr. Aub did, that lymphoma was now invading the lungs but that it should have responded to radiation therapy since the lymphoma in the stomach had responded so well. We were much surprised when the lungs did not clear after x-ray therapy. Perhaps that favors Dr. Bauer's suggestion.

CLINICAL DIAGNOSIS

Lymphoma of lungs.

DR. JOSEPH C. AUB'S DIAGNOSES

Lymphoma of stomach.
?Lymphoma of lungs.

ANATOMICAL DIAGNOSES

Amyloidosis of lung, severe.
Lymphoma of stomach, cured by x-ray treatment.
Amyloidosis of stomach, larynx, trachea, lymph nodes and spleen.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This man died in Providence and was autopsied at the Rhode Island Hospital. Since he had been followed here for so long, Dr. Herbert Fanger, the pathologist to the Rhode Island Hospital, very kindly sent us the autopsy protocol and microscopical slides.

Both lungs were very voluminous, filled the chest cavity and were very firm. Each weighed over 3000 gm.; normally a lung weighs 300 to 400 gm. so that is almost ten times the normal weight. As was expected there was very little air left in the lungs. The densities seen in the x-ray film were made up of grayish-white infiltrating tissue. Microscopically, this material was located around blood vessels, involving their walls along the alveolar septums, and also as solid masses — findings classic for amyloidosis (Fig. 4). We could find no evidence of lymphoma anywhere in the lungs. The entire tracheal wall was replaced with amyloid, as was the larynx. The lymph nodes in many places were almost entirely replaced with amyloid — a finding often seen in so-called primary amyloidosis. There was no evidence of lymphoma in the lymph nodes.

This patient was operated on by Dr. Leland McKittrick; we included his long operative note to show where the lymphoma had been. The whole stomach at operation seemed to be infiltrated. Dr. McKittrick took the biopsy from the serosa of the stomach. At autopsy seven years later the serosa of the stomach was perfectly free from lymphocytes and gave no evidence of lymphoma. This was true also in the bowel. In other words we have good evidence that the lymphoma really was cured by the x-ray treatment. The submucosa of the stomach, however, was infiltrated with amyloid.

You are all probably wondering now whether the patient really had had lymphoma; so did we. On review of the slides, however, there was no question in anybody's mind — and I have shown this to half a dozen pathologists — that there was an extensive lymphomatous infiltration, with many cells of the lymphoblastic type, mitotic figures and complete distortion of architecture. Then, of course, we wondered whether he had had amyloidosis at that time, and sure enough there were small deposits of amyloid that we had not recognized because we were paying attention only to the lymphoma. In the biopsy from esophagoscopy done by Dr. Benedict we described the lymphomatous cells, mature lymphocytes in the esophageal mucosa, but did not recognize the pink-staining amyloid; we thought it was merely fibrous

tissue in among the lymphocytes. I think, therefore, that we have evidence that this man had not only lymphoma, from which he was cured because no evidence of lymphoma was found in the entire autopsy, but also amyloidosis at the time of the fifth admission when he was first biopsied. The amyloidosis progressed and involved the lungs. It was present in other portions of the body too. The liver, however, had no amyloid deposits, and the spleen had only a few.

DR. ALLEN G. BRAILEY: Are these two conditions related in any way?

DR. CASTLEMAN: I do not believe we have seen any cases here with the combination of malignant lymphoma of this type and amyloidosis.

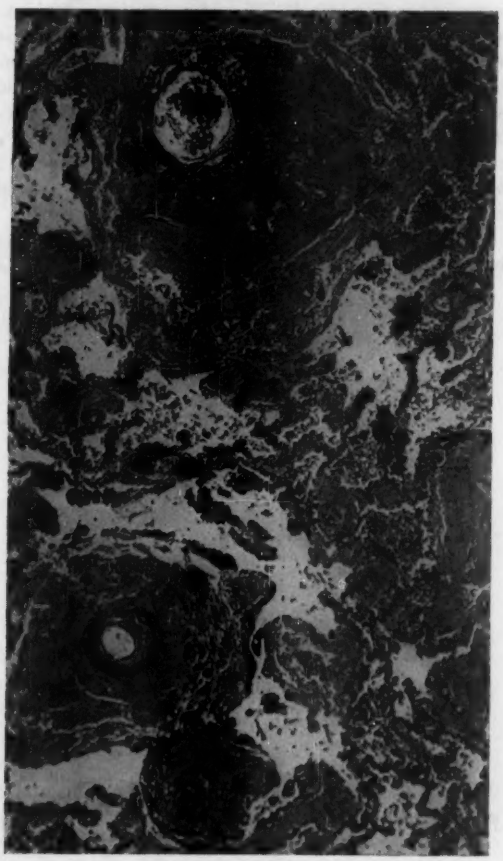

FIGURE 4.

Amyloidosis, however, has been reported in association with the Hodgkin type of lymphoma. Wallace et al.[1] reported 1 case and found 35 cases in the literature. We presented a case with this combination at a Clinicopathological Conference almost five years ago.[2] At that time Dr. Morgan looked up our cases and found that, of 60 patients with Hodgkin's disease, 5 also had amyloidosis.

This lung picture has interested the Department of Radiology and especially Dr. Wang. Should you like to say a word about amyloidosis in the lung?

DR. WANG: Recently, Dr. Laurence L. Robbins and I completed a study of amyloid disease from the roentgenologic viewpoint.[3] We attempted to discover the x-ray manifestations of this disease in various systems, such as the lungs, heart, gastrointestinal tract, spleen, liver and kidneys. We had seen 9 cases of amyloid disease of the lungs; 6 of those gave definite roentgenologic evidence of abnormality. We are extremely fortunate that, in the patient under discussion, we had complete roentgenologic studies from the very beginning. In the early stage of amyloid disease of the lung one can see merely thickening of the pulmonary markings, with stippling of the peripheral lung fields. In the intermediate stage of the disease one can see evidence of a miliary process, such as is seen in sarcoidosis, miliary tuberculosis or silicosis. In the late stage, when large amounts of amyloid are deposited in the lungs, the appearance may mimic lymphatic spread of carcinoma.

There is also hilar lymphadenopathy when the lymph nodes are filled with amyloid. We realize that these roentgenologic changes in the lungs secondary to amyloid deposition are not pathognomonic of the disease. However, in combination with the changes in various other systems, such as the heart, gastrointestinal tract, kidneys, liver and spleen, the possibility of amyloidosis should be raised, and the final diagnosis made by histologic examination.

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CASE 41232

PRESENTATION OF CASE

A thirty-eight-year-old Negro truck driver entered the hospital because of convulsive seizures.

Three months previously he had a severe sore throat accompanied by swollen, sore cervical lymph nodes. He was treated with penicillin and sulfonamides, and gradually improved over a period of two weeks. Ten days before admission a sore throat of milder degree recurred. He obtained relief by taking more sulfonamides, but three days later migratory aches in the shoulder, elbow, wrist, ankle and knee joints developed and lasted for about two days. There was no joint swelling or redness. There were no further symptoms until 4 a.m. of the day of admission, when he suddenly "blacked out" while sitting on the toilet. He regained consciousness and found himself slumped against the wall. He then felt normal and walked back to bed. Two hours later his wife

was awakened by snorting sounds and noticed that he was "stiff all over." She was unable to arouse him by shaking him. However, a few seconds later he regained consciousness. One and three hours later two similar tonic seizures occurred. Four more seizures occurred close to one another within the four hours immediately before admission. These lasted a minute or two, were preceded by blurring of vision and accompanied by incontinence of urine. The final one was followed by palpitation and marked weakness. There was no tongue biting or frothing of the mouth with the seizures, nor did diplopia, headache, speech difficulty or paresis follow them.

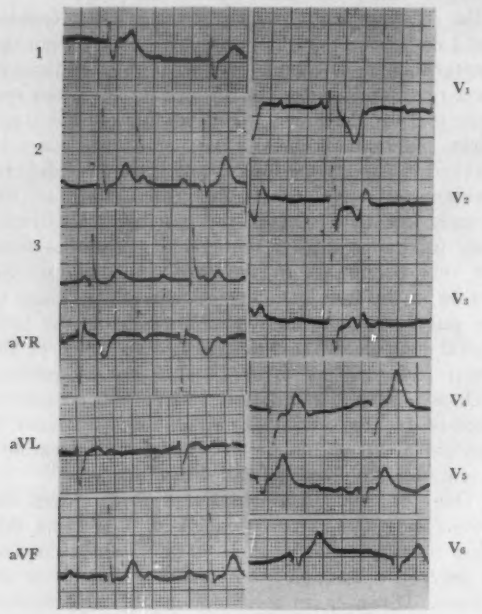

FIGURE 1.

As a youth the patient indulged in athletics. For the past five years he was somewhat short of breath on exertion and experienced occasional palpitation. He had never had convulsions, chorea or arthralgia before the present illness. He passed the physical examination for military service but was rejected because of "nerves." His appetite was poor for the last three months, during which he had lost 10 to 12 pounds.

Physical examination showed a man of slight build in no acute distress. The tonsils were enlarged but not inflamed. Several shotty nontender lymph nodes were palpable in the neck. The neck veins were flat. The lungs were clear. The heart was slow but regular. The point of maximum impulse was in the sixth interspace in the midclavicular line. The first mitral sound was loud, and the pulmonic second sound was accentuated and split. There was a Grade 2 to 3 harsh systolic murmur best heard along the left sternal border in the second and third interspaces, and accompanied by a thrill. A short Grade 1 systolic murmur was heard at the apex. One observer heard a diastolic rumble at the apex, and another heard a third heart sound but no diastolic murmur. The abdomen, extremities and reflexes were normal. The liver edge was percussed 2 fingerbreadths below the right costal margin, but neither liver nor spleen was palpable. There were no petechiae or splinter hemorrhages.

The temperature was 101°F., the pulse 50, and the respirations 18. The blood pressure was 130 systolic, 70 diastolic.

Urinalysis revealed occasional granular and numerous hyaline casts but was otherwise negative. Examination of the blood showed a white-cell count of 17,100, with 73 per cent neutrophils, and a hemoglobin of 12.1 gm. per 100 cc. Blood chemical determinations were normal. The sedimentation rate (corrected) was 15 mm. per hour. A stool guaiac test was negative. Throat culture grew abundant alpha-hemolytic streptococci and occasional nonhemolytic streptococci. A blood culture was negative. An electrocardiogram showed an atrial rate of 140 and a ventricular rate of 55. The QRS interval was 0.12 second; S waves were broad in Leads V_5 and V_6 and RR_1 waves were present in Lead V_1 (Fig. 1).

During the day after admission the temperature rose to 104°F., and watery diarrhea developed. The patient complained of the sudden onset of right-flank pain followed by mild tenderness in the right costovertebral angle. On the third day the diarrhea subsided. On the morning of the fourth day numbness and clumsiness of the right arm suddenly developed, but improved during the day. Neurologic examination revealed slight impairment of skilled movements, vibratory, postural and tactile senses of the right arm, without motor, temperature or pinprick impairment. At this time the systolic murmur in the third inter-

FIGURE 2. *Posteroanterior Roentgenogram of the Chest. The lungs are clear; the heart appears to be generally enlarged to a moderate degree.*

costal space was noted to be much less intense than on admission. On the fifth day the patient was seen in what appeared to be the termination of a convulsive seizure from which he went into semicoma. Neurologic examination now showed left-sided facial weakness and flaccidity of the left arm and leg. He was confused and uttered a few unintelligible words. Movements of the right side were purposeless and clumsy. Reflexes on the right were normal, and those on the left decreased. The eyes moved conjugately in all directions.

Laboratory data accumulated during the five hospital days included corrected sedimentation rates of

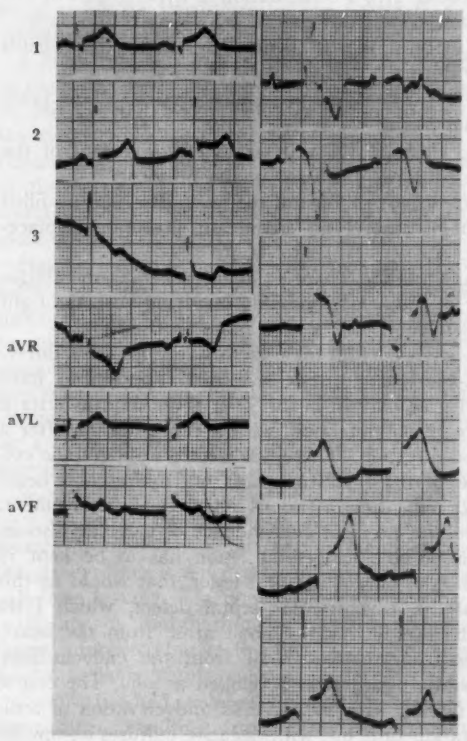

FIGURE 3.

34 and 35 mm. per hour, five additional negative blood cultures, negative urine and cerebrospinal-fluid cultures and negative Widal and blood Hinton tests. Stool culture revealed abundant alpha-hemolytic streptococci, but no enteric pathogens. After the onset of semicoma a lumbar puncture disclosed an initial cerebrospinal-fluid pressure equivalent to 200 mm. of water and a very slightly xanthochromic fluid. An x-ray film of the chest demonstrated enlargement of the left atrium and probably of the right ventricle (Fig. 2). The lung fields were clear, and there was no evidence of fluid in either pleural cavity. A skull film showed some calcification of the falx cerebri.

Repeated electrocardiograms disclosed a changing picture. On the second day the atrial rate was 125, and the ventricular rate 65. On the third day there was atrial flutter, with a ventricular rate of 75 and a QRS interval of 0.14 second, with slurring and notching. The ST segment was elevated in Leads 1, 2, aVL and V_2 through V_6. On the fifth day there was normal sinus rhythm in Leads 2 and 3 and complete atrioventricular dissociation in most other leads. The ST segment was elevated in Leads 1, 2, 3, aVL, aVF and V_3 through V_6. The T waves were inverted in Leads V_1, V_2 and V_3. There was slurring and notching of the QRS segment (Fig. 3). The last tracing in the afternoon of the same day showed similar findings except for the presence of complete heart block in all leads. Treatment was at first supportive. On the fifth hospital day anticoagulants, adrenocortical hormones and antibiotics were begun, but coma deepened, urinary output decreased, and the patient died the next day.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD J. CLARK*: This patient's illness appears to have been primarily febrile in both its inception and course. Three months before entry he had a severe throat infection lasting two weeks that responded to treatment with penicillin and sulfonamides. Ten days before entry he had another sore throat, again treated with sulfonamides. Three days later for two days he had migratory joint pains without swelling. Did this represent the onset of acute rheumatic fever, or was this possibly a sensitivity reaction perhaps to sulfonamides? Neither possibility can de denied. The symptoms subsided rapidly without treatment for frank rheumatic fever.

The next important point is the onset of syncopal spells. Did these represent a primary neurologic lesion or were they evidence of an Adams–Stokes type of episode associated with the heart block that he had on admission? Because of their brief nature and lack of associated neurologic signs at this time, I shall attribute them to the heart block.

When he was admitted to the hospital, the heart was not enlarged, but there was a Grade 2 to 3 harsh systolic murmur in the third left interspace associated with a thrill. He had presumably had a negative physical examination for military service at some previous time. We do not know when that was. As many of us know, service examinations can be quite misleading, and yet, if the patient had anything approaching a Grade 3 pulmonary systolic murmur associated with a thrill, it is surprising that this would have been overlooked. The description of the murmur suggests one of two things: a congenital lesion such as pulmonary stenosis, an atrial septal defect, or possibly a high ventricular septal defect, or a loud functional pulmonary systolic murmur as seen in some cases of febrile disease. The presence of the thrill confirms the intensity of the murmur and lends weight to the assumption of a congenital lesion. The presumed absence of the murmur at the examination

*Associate physician, Massachusetts General Hospital.

for military service argues against this. On the fourth hospital day this murmur was much less intense. If the patient was going into shock or into heart failure the murmur could have become less intense on this basis. Can anyone tell us more about the murmurs?

DR. B. FRAME: On admission, there was a Grade 2 systolic murmur accompanied by a thrill in the left second and third intercostal spaces. Over the next three or four days this murmur decreased in intensity, and the thrill disappeared. He continued to have a Grade 1 systolic murmur at the apex and also a third heart sound there. The pulmonic second sound remained very loud and split; the mitral first sound was loud, but not snapping.

DR. CLARK: A Grade 2 pulmonic systolic murmur is not too impressive by itself. I am inclined to dismiss this as evidence of a congenital lesion, but in this I may well be wrong. The short Grade 1 apical systolic murmur and the third sound or questionable transient apical diastolic murmur in themselves do not indicate too much in a febrile patient. The accentuated pulmonic second sound may have been of importance in connection with some involvement of the right ventricle.

The electrocardiograms taken after arrival at the hospital give important but not entirely specific information (Fig. 1 and 3). I looked at a few of them this morning. They are certainly consistent with an atrioventricular block and dissociation, with a prolonged QRS interval, probably of the right-bundle-branch type, which may indicate either hypertrophy of the right ventricle or myocardial damage, with a defect of interventricular conduction of the right-bundle-branch type. The one clue might be in the section of the tracing showing the normal rhythm in Leads 2 and 3 mentioned subsequently. I should judge that the interventricular-conduction defect continued, indicating a basic bundle-branch block. There is the interesting question of what the ST-segment elevation described on the fourth and fifth days means. This elevation occurred first in some of the leads and then spread to other leads. That in itself is highly suggestive of pericarditis; however, I must keep in mind that, in the presence of bundle-branch block, ST-segment elevations can occur independently of myocardial infarction or pericarditis.

Other important evidence is the occurrence of what I shall take to have been embolic phenomena. I judge that he had an infarct of the right kidney and possibly a small mesenteric infarct on the second hospital day, followed on the fourth day and again on the fifth day by cerebral emboli, the second of which was major, resulting in a considerable area of infarction. This could explain the elevated cerebrospinal-fluid pressure and the slightly xanthochromic fluid. May we look at the x-ray films at this point? I gather that the skull films show nothing of any significance.

DR. C. C. WANG: Examination of the chest shows perfectly clear lungs. The heart is generally enlarged, and the enlargement appears chiefly to involve the ventricles (Fig. 2). I do not see any definite significant enlargement of the left atrium. The main pulmonary artery, seen on the right anterior oblique projection, appears somewhat more prominent than usual, but the hilar shadows and pulmonary vessels are within normal limits.

DR. CLARK: Do you agree that by this examination we can probably rule out any likelihood of congenital pulmonary stenosis and can certainly rule out an atrial septal defect?

DR. WANG: I do.

DR. CLARK: The most common congenital lesion that could give a combination of hypertrophy of this type and conduction defects is a defect of the ventricular septum. Were the markings in the lung fields fairly normal?

DR. WANG: The pulmonary markings are fairly normal in size.

DR. CLARK: Do you see any enlargement of the left atrium, as described in the protocol?

DR. WANG: I do not see any. The barium-filled esophagus shows no significant posterior displacement.

DR. CLARK: There is, then, generalized enlargement of the heart, probably involving both the right and left ventricles, a little more on the right.

To what may all these factors add up? This thirty-eight-year-old normotensive man appears to have failed gradually in health over three months after a severe throat infection, with a rapid decline after a second infection. There was electrocardiographic evidence of major disturbances of rhythm and heart block, indicating a serious myocardial involvement. There was no clear-cut evidence of valvular disease, but a possible congenital lesion has to be kept in mind. The only congenital lesion that would fit this picture is a ventricular septal defect, which I do not believe he had. Emboli arose from the heart, either from the valves or from the endocardium. Probably, pericarditis developed as well. The course was febrile, with leukocytosis and elevation of sedimentation rate, but with negative cultures except for the presence of streptococci in the throat.

Did he have acute rheumatic fever set off by the streptococcal throat infection? This would explain much of the picture except for the embolic phenomena. I understand that emboli from acute rheumatic vegetations alone are practically never seen and there was no clear-cut evidence for chronic heart failure that would make me suspect emboli arising from the left atrium. Complete heart block from acute rheumatic fever is extremely rare. There has recently been one such case in the hospital, which Dr. Edward F. Bland described as unique. A similar case has occurred at the House of the Good Samaritan. Perhaps this is it, but I doubt it. There may prove to have been rheumatic carditis, but this alone does not satisfy me for the entire explanation in this case.

What about bacterial endocarditis? This seems to

have been a choice well up on the list of diagnoses considered, and it may be the obvious answer, but to me it does not quite fit all the facts. We know all too well that positive cultures may not be found and that other classic signs may be missing. The course was rapid for bacterial endocarditis unless I assume an acute infection. In such a case I think cultures should have been positive. Onset with heart block is inconsistent with bacterial endocarditis unless I assume a concomitant rheumatic infection. There was no certain evidence of congenital or valvular disease on which this process was imposed unless there was minimal mitral regurgitation. Possibly, I should stop with a diagnosis of acute rheumatic carditis and associated bacterial endocarditis, but I strongly suspect something more unusual.

I think that this process probably represented one of the more exotic and rare varieties of heart disease. In this group I should consider one of the connective-tissue processes such as disseminated lupus erythematosus possibly, with a verrucous endocarditis of the Libman–Sacks variety. I should be happier about this if the patient had had a leukopenia and more anemia.

Having missed a case of subendocardial fibroelastosis, I must mention this. Such a process commonly produces arrhythmias and emboli and has been shown to mimic various types of heart disease; however, dyspnea from myocardial failure is a very common symptom in this process, the course is usually more chronic, and evidence of acute infection is less. So far as I know, pericarditis has not been reported in association with it.

So-called Fiedler's interstitial myocarditis can produce certain of these findings, and in this condition mural thrombi and emboli are common but again the pericardium is not ordinarily involved.

Before leaving infections I should mention the possibility of diphtheritic myocarditis after acute throat infections, but in this day such an occurrence is most unlikely in this region.

Finally, I should consider one of the causes of severe myocarditis, resulting from either sulfonamide or penicillin sensitivity, that have been demonstrated here on rare occasions.

If I have to choose I shall put disseminated lupus erythematosus first, but shall be surprised at nothing that may be demonstrated.

DR. WALTER BAUER: I saw this patient on one occasion. I thought the clinical picture was due to some type of diffuse vasculitis. Because of the cerebral manifestations I favored a diagnosis of lupus erythematosus; however, I had to admit that there were insufficient specific findings to permit an accurate interpretation of the type of vasculitis present. I entertained some of the other diagnostic possibilities mentioned by Dr. Clark, such as endocardial fibrosis and rheumatic and Fiedler's myocarditis, but found it difficult to prove their presence.

DR. HOWARD B. SPRAGUE: This patient entered the hospital on my service. I was alert to the possibility of rheumatic heart block because the patient to whom Dr. Clark referred was also on my service. I showed that patient at Medical Grand Rounds as a unique example of Adams–Stokes attacks during acute rheumatic fever. Although one electrocardiogram of complete atrioventricular block with rheumatic fever was found at the House of the Good Samaritan by Craige and his associates,[1] that patient did not have syncopal attacks. We thought in the present case, before any of the laboratory data were available, that we should try to make a diagnosis, and we argued as Dr. Clark has: from the presence of incomplete right-bundle-block, the story of five years of cardiac disability or breathlessness, the known susceptibility of patients with interatrial septal defects to rheumatic fever and the evidence of increased pulmonary circulation as suggested by the pulmonic systolic murmur and thrill, we made a tentative diagnosis of rheumatic myocarditis complicating an atrial septal defect. When we saw the x-ray films with no evidence of increased pulmonary circulation and when definite neurologic signs, which were absent before, began to develop, we were forced to decide that this was some other infection — bacterial endocarditis or myocarditis.

The decision about therapy, of course, was very difficult. Our previous patient with a complete heart block was very rapidly helped by cortisone and Isuprel (isopropylarterenol) sublingually. We did not dare to start this therapy on this patient before we had several blood cultures, which later were all reported negative. As Dr. Clark said, the final therapy was one of desperation, in which both antibiotics and cortisone were used. May I say that Dr. Clark's comment about diphtheritic myocarditis is unhappily not entirely correct? According to a recent statement by Dr. Conrad Wesselhoeft[2] sore throats are being indiscriminately treated with penicillin, thus disturbing the bacterial flora and cultural characteristics but not curing the disease, and diphtheria is being missed, with fatal results.

CLINICAL DIAGNOSES

Acute myocarditis.
Embolism of brain.

DR. RICHARD J. CLARK'S DIAGNOSES

Disseminated lupus erythematosus, with pericarditis; myocarditis, diffuse, and endocarditis.
Multiple emboli.

ANATOMICAL DIAGNOSES

Pancarditis, severe, undetermined etiology.
Embolus, right middle cerebral artery, with infarction.
Embolus, left kidney, with infarction.

Pathological Discussion

Dr. Richard B. Cohen: At autopsy the heart weighed 360 gm.; the chambers were all slightly dilated, and there was a mild fibrinous pericarditis with some cloudy pericardial fluid. There was no evidence of scarring of the valves, and the myocardium was not impressively altered. Microscopical examination, however, revealed a severe pancarditis involving all the chambers of the heart. Most striking was the severe myocarditis. The muscle was infiltrated by large numbers of histiocytes and mononuclear cells, with lesser numbers of neutrophils and an occasional eosinophil. Necrotic fibers and groups of fibers were frequent and were often replaced by granulation tissue (Fig. 4). The pericardium was extensively infiltrated by a similar exudate, as was

Figure 4.

the endocardium. In the endocardium the infiltrate resulted in the formation of occasional verrucalike structures, and fragments of old and recent thrombi were adherent to the endocardial surface. In several areas, particularly on the pericardium, there were foci of acidophilic degeneration of collagen that suggested fibrinoid necrosis.

In evaluating the case on the basis of these findings the pathologist is faced with as difficult a differential diagnosis as the clinician is. No specific infective agent, either bacterial or parasitic, was found. The group of idiopathic myocarditides, of which Fiedler's myocarditis is a member, was excluded on the basis of the severe pericarditis and endocarditis. The postpharyngitic myocarditis described by Gore and Saphir[3] was excluded on the same basis. A myocarditis resulting from drug sensitivity was thought unlikely on the basis of the pericardial and endocardial reaction and the absence of any other stigmas of sensitivity reactions. A diagnosis of diphtheritic myocarditis was not compatible with the histologic picture. To make a diagnosis of rheumatic pancarditis and to be fairly certain of one's ground one must demonstrate Aschoff bodies. There were none in this heart. There were, however, large histiocytes with basophilic cytoplasm that resembled Aschoff cells, and areas of fibrinoid necrosis, which is a feature of collagen disease. There was no evidence in any organ of a vasculitis suggestive of lupus erythematosus or polyarteritis nodosa. The pathologist is unable in this case to assign a specific name to this disease or to classify it definitely in a particular group. We consider it a severe pancarditis of undetermined etiology. It seems closely related on morphologic grounds to the pancarditis that develops during the course of rheumatic disease, and often in some of the other collagen diseases. It is possible that the rarity of heart block in rheumatic carditis is dependent on the fact that massive muscle-fiber necrosis is not typical of rheumatic myocarditis. Extensive necrosis was present in this case and probably accounted for the block.

This carditis was the source of emboli to the right middle cerebral artery, resulting in extensive infarction of the right cerebral hemisphere, and in embolization and infarction of the kidneys.

Dr. Bauer: Were there no hematoxylin bodies anywhere?

Dr. Cohen: There were no hematoxylin bodies; we looked for them carefully.

Dr. Clark: Were there thrombi in the endocardium?

Dr. Cohen: On gross examination there was no definite thrombosis, but on microscopical examination there were small fragments of thrombotic tissue adherent to the endocardium that were probably the source of the emboli.

Dr. Bauer: Was an L.E.-cell preparation ever done?

Dr. Cohen: I do not believe so.

Dr. Clark: Was there any suggestion of a sensitivity reaction?

Dr. Cohen: We excluded drug-sensitivity reactions because they are not characterized by so severe an endocardial or pericardial reaction. I should have preferred in a sensitivity reaction to see evidence of a vasculitis.

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DEVELOPMENT OF HEALTH RESOURCES

THE Subcommittee on Hospital Services of the Health Resources Advisory Committee of the Office of Defense Mobilization has issued a report embodying the results of a study of the care of patients with long-term and of those with short-term illnesses. The two main considerations involved, according to the report, are to make certain that each patient receives the right services at the right time, and to determine what organization of these services will be the most economical of personnel. Viewed in relation to mobilization readiness the solution of these problems would restore patients to maximum function in a minimum of time and make possible more effective utilization of the health workers involved.

In regard to long-term illnesses in particular, the probability is recognized that all patients need, in addition to individualized rehabilitation services, re-evaluation services at appropriate intervals. The long-term patients are divided into two categories: the chronically ill, distinguished by their continuing need for access to the same sort of therapeutic services that are needed by short-term patients, and those with physical defects resulting from acute disease or from injury, with their differing problems. Patients in the second category are not considered as needing continuing access to intensive diagnostic and therapeutic services after the acute situation has been resolved.

The long-term patients are classified as requiring skilled care for short periods rather than prolonged, less skilled custodial care; the application of this principle requires the development of a "philosophy of rehabilitation" — a rehabilitation mindedness on the part of physician, hospital, administrators and governing boards and other health personnel.

The Subcommittee puts its recommendations in the form of five requests that the Health Resources Advisory Committee should make.

It should request that ways and means of indoctrinating medical students in the philosophy of rehabilitation be considered by the deans of medical schools, through the Association of Medical Colleges. It should "request the directors of university programs in hospital administration, through the Association of University Programs in Hospital Administration, to give greater emphasis to the philosophy of rehabilitation." It should request the American Hospital Association to promote in its publications the same philosophy and "recognition of the need for comprehensive programs under centralized or coordinated management." It should request directors of nursing education programs, through the National League for Nursing, to consider methods of accomplishing a similar indoctrination of nurses, and it should request progress reports from the groups that are already working on these problems.

The widely used word "rehabilitation" is obviously based on "habilitation," with its more restricted

meaning. To habilitate is "To fit out or equip for working, as a mine." "To clothe; dress." To rehabilitate is "To restore to a former capacity; reinstate." "To restore to good repute; vindicate." "To restore to solvency, efficiency, etc." "To fit to make one's livelihood again; as to *rehabilitate* disabled soldiers." It is with all these definitions that a true program of rehabilitation is concerned.

NEW HARVARD SURGICAL UNIT

HARVARD Medical School, with the re-establishment of a surgical unit at the Boston City Hospital and the creation this summer of the new Sears Surgical Laboratory, will again participate in surgical research, teaching and patient care at that institution.

DR. J. ENGLEBERT DUNPHY

This triad of service is made possible largely by the bequest of Charles H. Tyler, of Boston, who died in 1931, leaving a public charitable trust as a memorial to the late Dr. George G. Sears, formerly clinical professor of medicine at Harvard and a trustee of the Hospital. The fund now amounts to well over $1,500,000.

Harvard teaching of surgery at Boston City Hospital is the School's oldest link with the institution. It began with the founding of the Hospital in 1861, when Dr. David William Cheever took over this function and continued it until his retirement as professor of surgery in 1892. Others succeeded him until finally, in 1942, Harvard found it necessary to abandon its surgical teaching there.

The new unit, as Dean Berry points out, will relate to the Hospital much as do the existing Harvard Medical and Neurological Units. The former, centered in the Thorndike Memorial Laboratory, established in 1923, is under the direction of Dr. William B. Castle; the Neurological Unit, established in 1928, is directed by Dr. Derek E. Denny-Brown.

Dr. J. Englebert Dunphy will be Harvard professor of surgery and director of the new unit when it opens in July, with Dr. Charles C. Lund as surgeon-in-chief.

Born in Northampton, Massachusetts, in 1908, Dr. Dunphy graduated from Holy Cross in 1929 and from Harvard Medical School in 1933. After serving as intern and surgical resident at the Peter Bent Brigham Hospital he became a fellow at the Lahey Clinic and resident surgeon at the Hospital. He was in the Army Medical Corps from 1940 to 1946, when he retired as lieutenant colonel. During this period, from 1942 to 1945, he was attached to the Fifth General Hospital — the Harvard Unit — serving as chief of the surgical service from 1943 until 1945, when he was appointed chief consultant in surgery for the Oise Base Section. He was awarded the Bronze Star and was made a commander of the Order of Public Health by the French government.

Dr. Dunphy is currently clinical professor of surgery at Harvard, surgeon at the Peter Bent Brigham Hospital, chief consultant in surgery for the Veterans Administration in the New England and New York area, and special consultant to the surgeon general of the Army. Not the least among his various other memberships, assignments and miscellaneous honors is the position he holds on the editorial board of the *Journal*.

GOLDEN YEARS

FIFTY years ago, during the year 1905, a total of 212 physicians whose average age at the time was twenty-seven were admitted to membership in the Massachusetts Medical Society. On Tuesday afternoon, May 17, this year, as a feature of the one hundred and seventy-fourth annual meeting of the Society, 35 members of the "Class of 1905" were honored for having reached the golden anniversary of Society fellowship.

The youngest of these 35 physicians (with the unquestionable exception of the two women physicians in the group, whose birthdays are not, naturally, recorded in the Society's files) is seventy-three. The oldest is eighty-two.

Eleven of the group are general practitioners, the others representing eleven different specialties. One of the physicians is a past president of the Society. Another had the honor of being criticized for "commercializing surgery" when he showed, back in 1913,

what was then perhaps the first motion picture of a surgical operation. Still another was a pioneer in the control of venereal disease.

Five of the physicians sired 6 physicians — a remarkably good percentage, considering that the great majority of the offspring of this year's Golden Fellows are women.

The Society cannot help being warmly and enviably proud of its fifty-year members. Their immeasurable contributions to the practice and profession of medicine, despite the increase in man's life span, will be equalled by few of those who, reading this editorial, view their own fiftieth anniversary in the Society as the milestone in their careers that is well nigh unattainable; for as they know in their hearts, it is a blessing reserved for only the hardy, hearty and righteous.

STUDENT AWARDS

THE *Journal's* prize-essay competition for fourth-year medical students met with an unusual response this year, a greater number of papers being submitted than ever before in the seven years since the contest was started. This increased interest may be partly accounted for by the fact that the number of student subscribers has risen from an average of well under 4000 in 1948 to a peak of almost 7000 so far in 1955. The task of the judges was correspondingly greater, and their decisions have just been reported at the time of this writing.

When the identities of the prize winners were revealed their geographic distribution became also a matter of interest. The winner of the first prize, of $100, is Milton Wigod, at the time a fourth-year student and extern in pathology at the Medical College of Virginia, in Richmond. His essay on "Idiopathic Pulmonary Hemosiderosis" will appear as a special article in a subsequent issue of the *Journal.* The winner of the second prize, of $25, is Leslie E. Rudolf, of Cornell University Medical College, who reported and discussed a case of "Hyponatremia in a Patient Following Paracentesis." Bradley E. Brownlow, a fourth-year student at Western Reserve University School of Medicine, in Cleveland, was awarded the third prize of a two-year subscription to the *Journal.* His essay was submitted under the title "Myotonia: Delay in diagnosis because of possible hypoparathyroidism accompanying surgical athyria: report of a case."

The competition, it will be remembered, is based on the reporting and discussion of a case that the author has had assigned to him as part of his regular academic duties. Preparing the subject for the competition is therefore not very far out of line with his routine work. The interest that has been shown and the general excellence of the papers submitted speaks well for the inspiring quality of modern medical pedagogy.

Drs. Homans, Storer, Lewis and Adams of Boston, were the guests of the [Rhode Island] Society, and their presence and remarks at the annual dinner, contributed largely to the intellectual festivities of the occasion.

Boston M. & S. J., *June 14, 1855*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

KEAY—Harry C. Keay, M.D., of Sterling, died on April 24. He was in his eighty-first year.

Dr. Keay received his degree from Dartmouth Medical School in 1896. He was formerly a member of the staff of the Clinton Hospital.

He is survived by his brother.

MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH

COMMUNITY PROGRAM FOR MENTALLY RETARDED SCHOOL CHILDREN IN MASSACHUSETTS

In 1952 the Massachusetts Legislature recognized the need for providing additional facilities for retarded children including the more severely handicapped. A special commission was directed to study the number of retarded children in the Commonwealth and the training facilities available for their instruction. It was also ordered to report to the General Court the results of its investigation with recommendations, together with drafts of legislation necessary to carry out such recommendations. This unpaid special commission consisted of a member of the Senate, a member of the House of Representatives, a representative from the Department of Mental Health, a representative of the Department of Education, a representative of the Massachusetts Association for the Advancement of Exceptional Children, Incorporated, and a representative of the Massachusetts Special Class Teachers Association. After careful and complete study and investigation, a report was filed with the Legislature in December, 1953. The Commission recognized first of all that it was the inalienable right of parents to keep their severely retarded children at home if they so desired. Secondly, although some of these children might need eventual placement, an extended period of home and community experience would facilitate a better evaluation of the true potential of the child. Thirdly, it was recognized that one can never tell until one tries how well a program will work. The Commission accepted the thesis that severely retarded children may be acceptable in a community situation.

The Commission proposed legislation, which was signed into law on May 28, 1954, providing among other things for a division of special education in the Department of Education. This division has been given supervision and direction of all special education supported in whole or in part by the Commonwealth. The legislation further defines the Division's responsibility in the program of special classes for the instruction of educable and trainable mentally retarded children. It also provides that half the cost of the expenses of the instruction, training and support, together with transportation of children in these special classes, will be reimbursed to the cities and towns by the Commonwealth on approval of the Department and certification by it that such classes meet the standards and requirements prescribed. This act also requires that the school committee of every city or town annually ascertain, under regulations prescribed by the Department of Education and the Department of Mental Health, the number of children retarded in mental development attending its public schools, or of school age and resident in the city or town. Such children must be placed in the following classifications. the educable mentally retarded; the trainable mentally retarded; and the custodial mentally retarded. The law directs also that at the beginning of each school year, the Committee of every town where there are 5 or more retarded children *shall* establish and of every city or town where there are fewer than 5 such children *may* establish special classes for the instruction of the educable mentally retarded and for the instruction of the trainable mentally retarded children according to their mental attainment under regulations prescribed by the two departments. Smaller cities and towns having fewer than 10 mentally retarded children may, with the approval of the Department of Education, join with another city or town to provide the necessary special classes.

* * *

Practical experience in organizing and conducting community training programs for severely retarded children has been gained by the Department of Mental Health since 1946, when the Walter E. Fernald School began its community school for trainable mentally retarded children, as reported by M. J. Farrell in his article, "Experimental Classes Lead to State-Wide Legislation" (*Mental Hospitals* 6:21, 1951). Home training classes for other communities were developed by the Department of Mental Health in 1946 and continued through this year. Experience indicates that severely retarded children can be kept in the community and trained to carry out simple tasks, to work in a group and to develop a modicum of socially acceptable behavior. Most important is the careful work with parents that must accompany the training program. Through the use of group technics with trained leaders parents can be helped to face their problem realistically, to dispell their fears and guilts and their feelings of isolation and inferiority.

The community class at the Walter E. Fernald School, Waverley, has been copied by many communities in Massachusetts. Several large school systems have already set aside school buildings for the special training classes. One of these, the Rollstone School in Fitchburg, has been designated as a research center for a projected interdepartmental research program. All school committees and superintendents are currently involved with the new program. Information concerning its administration has recently been distributed by the Division of Special Education of the Department of Education. The director, Mr. Philip Cashman, and his two supervisors, Miss Roberta Kellogg and Mr. Nicholas Wells, are meeting with school people individually and in groups to plan the program, which will be well under way by next fall and in full swing by the fall of 1956. An interdepartmental committee of the departments of Mental Health and Education, with the technical assistance of the Department of Public Health, has written regulations and has prepared forms for the use of school personnel and the family physician in the initial educational and medical study of these children. The regulations and forms have been studied by the Committee on Mental Health of the Massachusetts Medical Society. Suggested amendments have been made. The physical-examination form is currently in the hands of the Committee on School Health of the Massachusetts Medical Society. Final approval is expected in May, 1955.

There are estimated to be approximately 59,000 retarded children of school age in Massachusetts. Only 6600 children are currently enrolled in special class programs. There are about 7500 persons of all ages in the four state schools. Most of these patients are not educable, or are educable with severe social and emotional disorders. Obviously, a concerted effort *on the community level* toward providing adequate means for early detection, thorough medical and educational study, adequate program planning and supervision is the only way to approach this mass disease problem. What is the proper role of the family physician, the school medical services and special clinical services in this program? Only experience can provide the final answer to this question. At present, the Department of Mental Health does have a plan that will serve to get the program started. The original traveling-school-clinic plan, under which mentally retarded children have been detected and studied for the past thirty-six years, consisted of a psychometric examination, physical examination and sociopsychiatric appraisal of the child in his school and family setting. Developments since 1919 in educational psychology, school-health services and mental-health practice have completely outmoded the traveling school clinic as a satisfactory system. Determination of the intellectual capacity of the child to

plan proper school placement is a natural and proper function of the school system itself. Most large school systems have their own testing services already. Under the new regulations individual psychometric examinations will, for the most part, be carried out by properly qualified school psychologists, preferably resident school psychologists. The medical study of these children, with careful testing of hearing and vision, is most properly carried out by the family physician, who can refer parents and children to specialized clinic services as indicated. The school physician can do the physical examination in the absence of the family doctor and usually has available equipment for tests of hearing and vision (Pure Tone Audiometry and Massachusetts Vision Chart).

The final determination of class placement of retarded children is the responsibility of the superintendent. He will have available the studies and recommendations of the school psychologist, the school-health services, the family physician and, if requested, the sociopsychiatric studies of the area mental-health center.

The area mental-health centers of the Division of Mental Hygiene, Massachusetts Department of Mental Health, are developing consultation services, available to school systems on request. Area centers in operation as of July, 1955, are as follows: Springfield Child Guidance Clinic; Chicopee–Holyoke–Northampton Area Mental Health Clinic; Worcester Youth Guidance Center; North-Central Mental Health Consultation Services (Athol, Gardner, Fitchburg, Leominster and 20 other towns in North-Central Massachusetts); Halloran Child Guidance Clinic at the Metropolitan State Hospital (Waltham, Watertown and Belmont); Greater Lowell Mental Health Center; Greater Lawrence Guidance Center; West End Guidance Center (Boston); Quincy Child Guidance Center; Franklin County Guidance Center; and Northern Berkshire Mental Health Center. These centers operate as "partnerships." The Department of Mental Health provides the basic professional team of psychiatrist director, psychologist, psychiatric social worker and mental-health consultant, and the community provides quarters, additional personnel, public education program and basic operating policies through the formation of a mental-health association. The basic clinic policies, such as eligibility, referral methods and fee schedule, are developed for each community by professional advisory committees composed in large part of physicians.

Retarded children are most conspicuous to school teachers, for they fail to learn the three R's in the primary grades and also give signs of social and emotional immaturity or retardation. For any given child the mental-health center may recommend further medical study, referral to the outpatient clinic of the state school, further psychiatric study at the center itself, or at some other appropriate clinic, or continued work with the school and parents by the consultant. The child may be tried in a new school setting. For the most part, the children fall into the following broad classifications:

The academically retarded child:

Average or good intelligence but so emotionally disturbed that he cannot adjust himself to the classroom situation, either socially or academically.

Average or above in intelligence but has a specific learning disability.

The educable retarded child:

Low scorer on intelligence testing, but gives signs of good potential and severe primary fault in personality development (the so-called pseudoretarded, atypical, autistic child and certain children labeled "childhood schizophrenic" are in this group).

Low scorer without special organic or emotional concomitants—the so-called simple familial (hereditary) retardation.

Low scorer with specific central-nervous-system disease (children with birth trauma, cerebral palsy, encephalitis or other brain trauma may fall into the educable group).

The trainable retarded child:

The child with mongolism.

The child with brain damage.

The "psychotic" child.

The child with other congenital defects.

Detection and suitable classification of these children are the proper function of the physician. The relative distribution of retarded children in the community in these groupings is as yet unknown. The traveling-school clinics since World War II have had referred to them increasingly large numbers of children with academic retardation only. Eighty-five per cent of children seen scored in the average or above-average intelligence range. It is this large group of children with emotional maladjustments that the child psychiatrist, child-guidance clinics and area-mental-health-center consultation and clinic programs are primarily designed to help. The children with true retardation, however, need no less a careful medical and educational study. The trainable group should be under the closest medical supervision, preferably in a specialized setting, such as that provided by the pediatrician, the pediatric neurologist or the outpatient facilities of the state schools. The continuing work, educative and supportive, with the parents of these children is an important and often neglected function of the medical discipline.*

Medicine, with its specialties, has a crucial part to play in this new program for the retarded child. The school physician and nurse, the family physician, the

*Material for physicians and parents concerning retarded children can be obtained from the following sources: National Association for Retarded Children, Incorporated, 129 East Fifty-Second Street, New York 22, New York; Boston Association for Retarded Children, Incorporated, 230 Boylston Street, Boston, Massachusetts.

pediatrician, the neurologist, the ophthalmologist, the otologist, the child psychiatrist, the public-health officer, the pathologist and the research physician are all involved.

Public-school systems throughout the Commonwealth have been ordered by the General Court to develop programs for these unfortunate children. The schools need the fullest understanding and support of their communities as they slowly, cautiously and with much trepidation move to carry out the provisions of the new law. The schools are completely dependent on the medical profession, both in a consultant capacity and in the screening and study phases of the program. Careful evaluation studies carried out over the next few years by medical groups will be needed to determine the final effectiveness of the program.

WARREN T. VAUGHAN, JR., M.D.
Director, Division of Mental Hygiene
MALCOLM J. FARRELL, M.D.
Superintendent, Walter E. Fernald State School

NONCLINICAL NOTES

HARVARD MEDICAL SCHOOL APPOINTMENTS

Announcement is made of the appointment by Harvard Medical School of Dr. David G. Cogan as professor of ophthalmology and of Dr. Walter M. Grant as associate professor of ophthalmology, both associated with the Howe Laboratory of the Massachusetts Eye and Ear Infirmary.

McLEAN HOSPITAL

Dr. Alfred H. Stanton, chief of the Psychiatric Closed Ward Section of the Boston Veterans Administration Hospital and assistant professor of psychiatry at Boston University School of Medicine, has been appointed psychiatrist-in-chief of the McLean Hospital, in Waverley, and associate professor of psychiatry at Harvard Medical School.

NOTICES

ANNOUNCEMENT

Dr. Jacob Peretsman announces the opening of his office for the practice of general surgery at 56 College Avenue, West Somerville, Massachusetts.

NEW ENGLAND HEALTH INSTITUTE PROGRAM

A three-day program on the aspects of health services, entitled "Lighthouses In A Changing World," sponsored by the New England Health Institute, will be held at Colby College, Waterville, Maine, August 30 and 31 and September 1.

Included among the topics will be local health services, changing patterns in family life, human relations in public health, teamwork in rehabilitation, tuberculosis control, accident prevention, juvenile delinquency, prevention and rehabilitation as applied to housing, prevention in dentistry and prevention of radioactive contamination of water and aquatic life.

Among the speakers will be Governor Edmund S. Muskie, of Maine, and Dr. O. Spurgeon English, head, Department of Psychiatry, Temple University School of Medicine.

MILITARY DISTRICT OF WASHINGTON POSITIONS FOR PHYSICIANS

Positions are available for a physician in roentgenology and in ophthalmology at the United States Army Dispensary, Pentagon Building, Military District of Washington, starting at $7,040 a year. The usual qualifications are necessary. Information may be obtained from the Public Information Service, Military District of Washington, Room 1513, Building T-7, Gravelly Point, Washington 25, D.C.

SOCIETY MEETINGS AND CONFERENCES

JUNE 11 and 12. American Electroencephalographic Society. Page 647, issue of April 14.
JUNE 13–30. Consultation Clinics for Crippled Children in Massachusetts. Page 963, issue of June 2.
JUNE 13–15. American Neurological Association. Page 689, issue of April 21.
JUNE 13–17. European Rheumatology Congress. Page 742, issue of April 28.
JUNE 15. Boston State Hospital Psychiatry Seminar. Page 461, issue of March 17.
JUNE 20. Annual Chaplains' Conference. Page 965, issue of June 2.
JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25, 1954.
JULY, AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.
JULY 1–4. International College of Surgeons. Page 828, issue of May 12.
JULY 10–16. Congress of Nobel Prize Winners. Page 510, issue of March 24.
JULY 11–15. Symposium on Tuberculosis. Page 509, issue of March 24.
AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
AUGUST 30 and 31 and SEPTEMBER 1. New England Health Institute Program. Notice above.
OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.
OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.
OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.
NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
NOVEMBER 29–DECEMBER 2. Interim Session of the American Medical Association. Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JUNE 16

THURSDAY, JUNE 16
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Thoracic Conference. Management of Acute and Chronic Pulmonary Infections. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, JUNE 17
Holiday

SATURDAY, JUNE 18
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten and staff. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Thibodeau and staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, JUNE 20
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Drs. Baty and Swenson. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

(Concluded on page xxvi)

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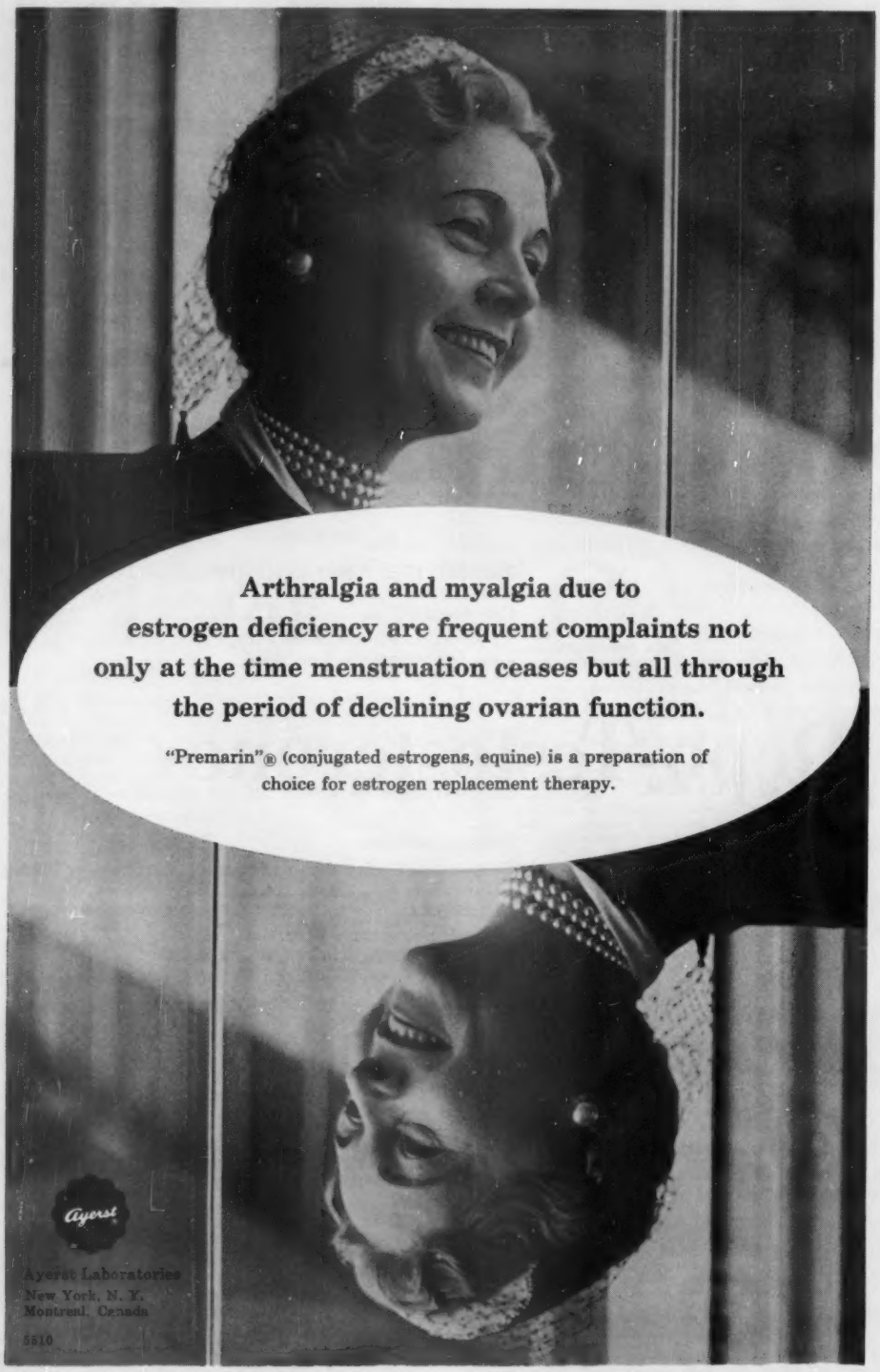
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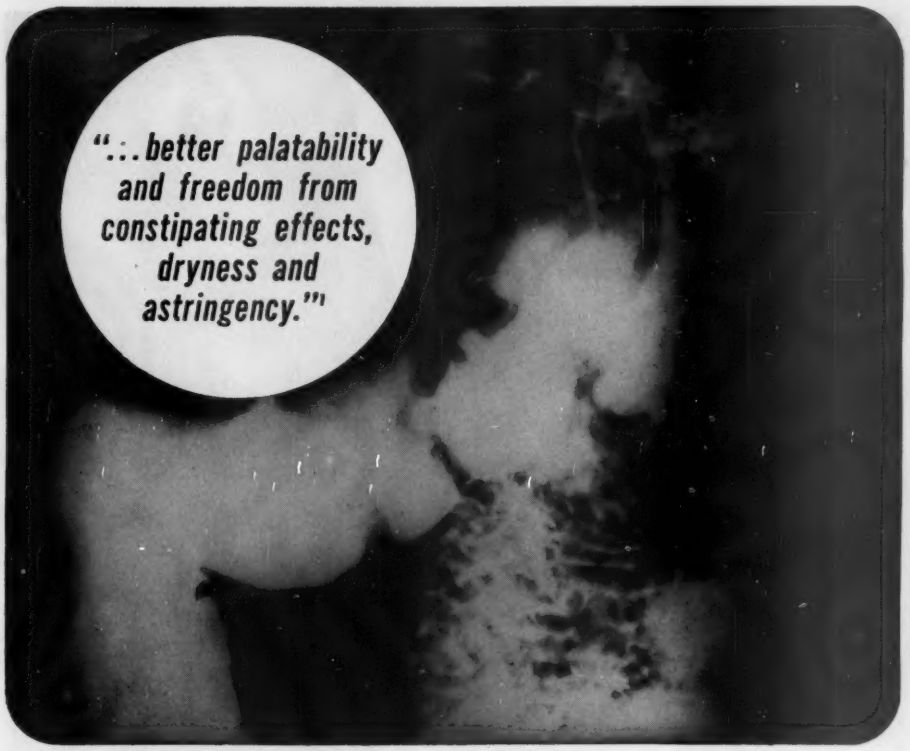

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1. Morrison, Samuel: Magnesium aluminum hydroxide gel in the antacid therapy of peptic ulcer, Am. J. of Gastroenterology 22:309 (Oct.) 1954.

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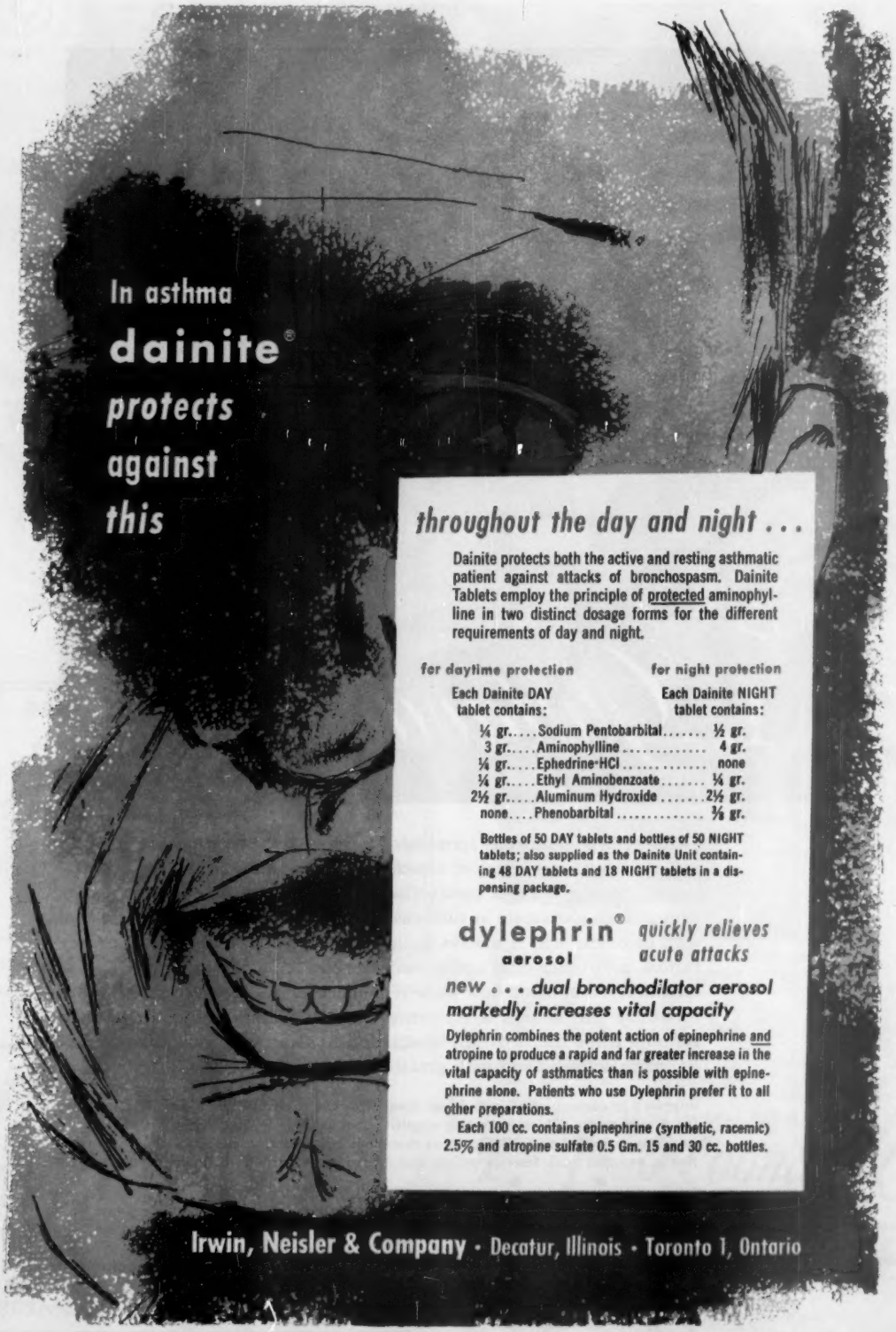

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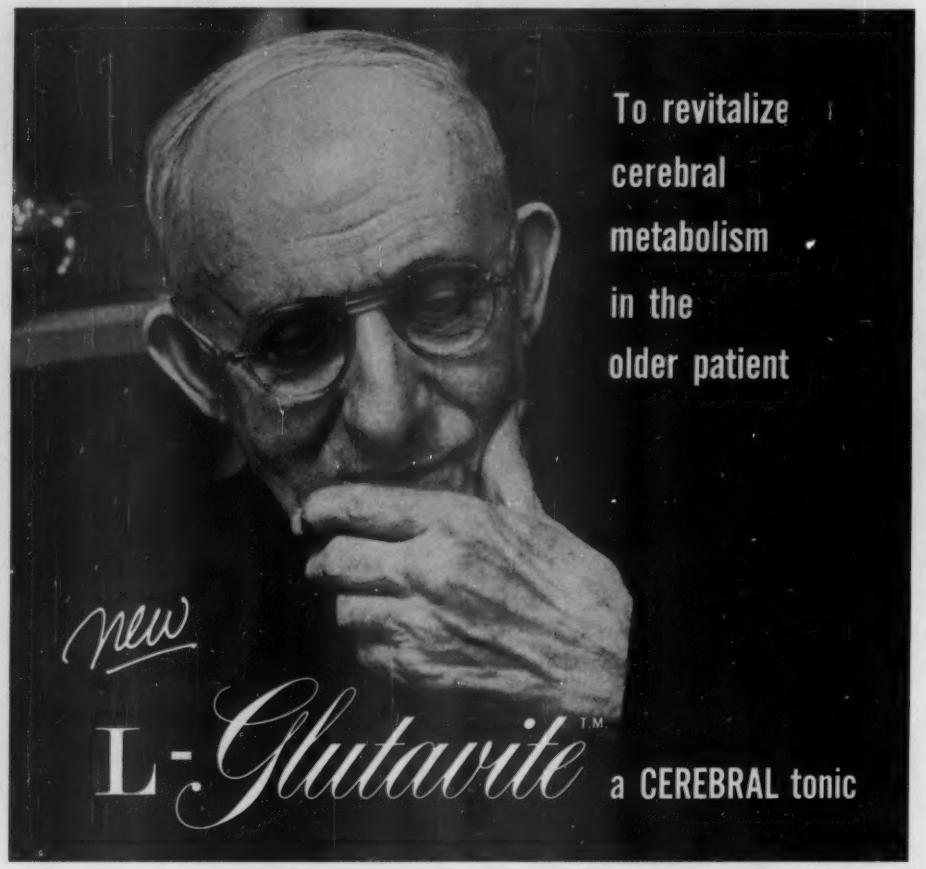

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1. Himwich H.E.: Paper presented at American Psychiatric Association meeting, St. Louis, May, 1954.
2. Lehmann, H.: 27th Annual Conference, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc., 1952. p. 587.

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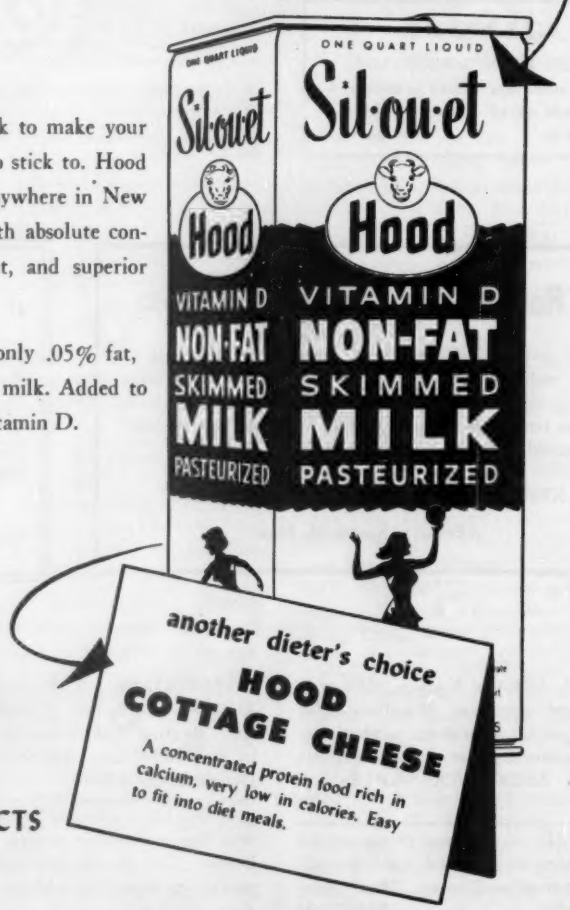

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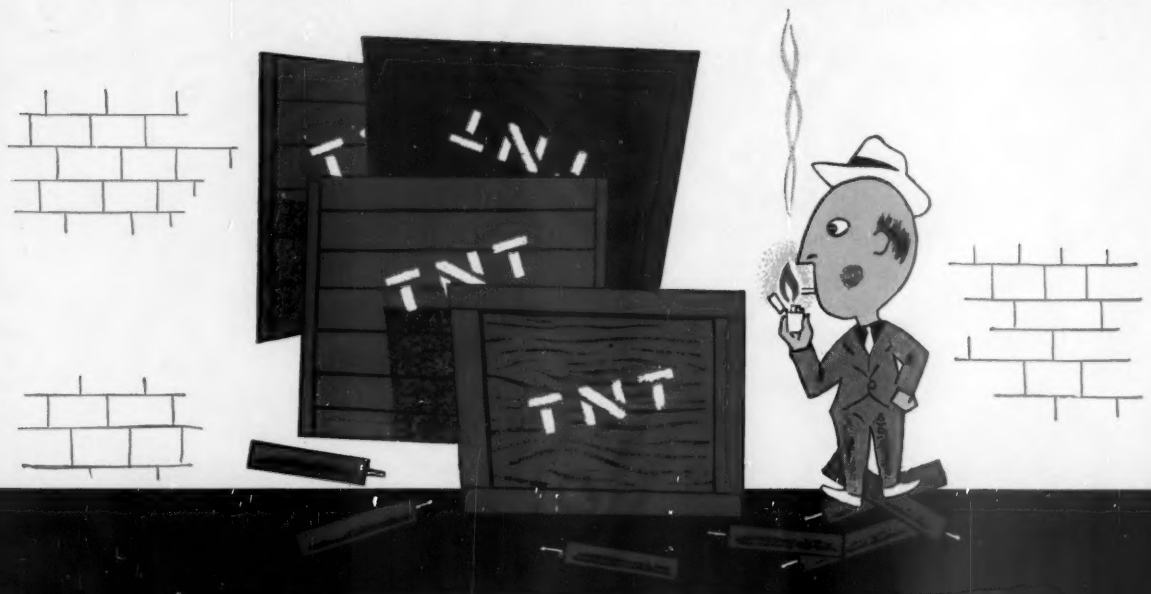

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